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14. ABSTRACT
Life support devices (e.g. heart pacemakers, ventilators, dialysis machines) are commonly thought to affect mainly their target organ system. This preliminary study attempts to determine the extent to which mechanical support of one organ system (lungs by mechanical ventilator) affects functions of other systems (heart and blood vessels).

We studied changes in cardio-respiratory interactions and in dynamics of cardiovascular system during scheduled transitions (spontaneous breathing trials, SBT) between mechanical and spontaneous ventilation in critically ill patients. This initial study

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Report Title

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We studied changes in cardio-respiratory interactions and in dynamics of cardiovascular system during scheduled transitions (spontaneous breathing trials, SBT) between mechanical and spontaneous ventilation in critically ill patients. This initial study population consisted of 13 patients admitted to a surgical intensive care unit (ICU) following surgery, trauma or complications who were judged candidates for liberation from the ventilator. We collected continuous respiratory, cardiac (ECG), and perfusion (blood pressure and pulse oximetry) signals of mechanically ventilated patients before, during and after SBT. The data were analyzed using spectral analysis, phase dynamics and entropy measures.

We found that the mechanical ventilation not only drives lung dynamics but also affects the dynamics of cardiac and vascular systems. Spontaneous cardiovascular rhythms are entrained by the mechanical ventilator and are drawn into synchrony. Sudden interruption of mechanical ventilation typically leads to rapid desynchronization. This synchronization is restored upon reinstitution of mechanical ventilation.

The initial data suggest that therapies intended to support one organ system may propagate unanticipated effects to other organ systems. Moreover, sustained therapies may disturb mechanisms that promote natural synchronization and variability and thereby adversely affect recovery of normal organ system interactions. We suggest that new measures and displays of synchronization not only could provide insight into the organ-organ coupling but also could yield information to optimize the function of devices used to support the critically ill patient.

List of papers submitted or published that acknowledge ARO support during this reporting period. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Cardiorespiratory Dynamics during Transitions between Mechanical and Spontaneous Ventilation in Intensive Care has been ACCEPTED for publication in the journal "COMPLEXITY"

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Anton Burykin	1.00
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Final Progress Report

Cardiorespiratory variability and synchronization in critical illness

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4. Statement of the problem studied

Many organ systems exhibit oscillatory (cyclic) behavior. The period of the oscillations can be long (menstrual cycling, diurnal temperature variation); intermediate (glucose concentration have long [90 min] and short [3-7 min] oscillations; and short (respiratory and cardiac cycling). Organ systems are coupled with one another via mechanical, neural and other mechanisms. Thus, the organism as a whole and respiratory and cardiovascular systems in particular can be conceptually viewed as nested systems of coupled oscillators. From this perspective, a support device (here, the mechanical ventilator) acts as an external driving force on a biological oscillator (here, the lungs driven by the ventilator musculature). Since the lungs are coupled to other organ systems (e.g. heart and vessels), it might be expected that mechanical ventilation propagates its effects beyond the lungs to other organ systems and thereby modifies their dynamics.

Detecting the presence and strength of the influence of one organ's cycling upon others is technically challenging. Biological oscillators are noisy and their couplings are typically nonlinear. Moreover, it is important from both a clinical and a biophysical standpoint to ask how external forcing of one of the oscillators changes the dynamics of other "oscillators" (organs) and the interactions (e.g. synchronization) among them. We have obtained preliminary results on the effect of the mechanical ventilation on cardiovascular dynamics and on cardiorespiratory synchronization. The focus of this initial study was the simplest case of a driving force - mechanical ventilation with constant frequency and amplitude.

The lungs and the cardiovascular systems are known to be coupled by several mechanisms that promote modulation and synchronization. For example, parasympathetic (vagal) influences cause the heart to beat faster during spontaneous inspiration and slower during exhalation. This phenomenon, which is called the respiratory sinus arrhythmia (RSA), is thought beneficial for pulmonary gas exchange and circulatory efficiency . From the point of view of physical theory of oscillation, RSA can be viewed as a frequency modulation of ECG by respiration. RSA is held

responsible for high frequency (0.15-0.4 Hz) peak in the heart rate power spectra. In addition to such modulations, another type of coupling has been recently described, namely the synchronization (locking) between instantaneous frequencies and phases of respiration and heartbeats. A reciprocal influence (cardiac activity upon ventilatory dynamics) has also been recently described. Cardioventilatory coupling (CVC) has been suggested as a regulatory mechanism separate from the RSA. The contribution of CVC is currently debated, since there appears to be near unidirectional interaction (i.e. lungs to heart) in human health after 6 months of age. Regardless, there likely exists at least indirect and reciprocal coupling of cardiac activity upon ventilatory performance.

Respiration can also modulate the vascular rhythms (e.g. oscillations of blood pressure or oxygen saturation in capillaries). There exists frequency modulation (variability of the distance between peaks in e.g. arterial blood pressure waveform) which is simply the consequence of the cardiac frequency modulation (RSA). Another modulation relates to the pressure variation in the thoracic cavity created by the respiratory chest motion. This variation causes baseline modulation of the blood pressure oscillation which can be assessed via monitoring of the systolic and diastolic pressure (maxima and minima of the blood pressure waveforms) variability. These two modulations are independent. Therefore, ventilation can entrain the vascular rhythms even in the absence of RSA or other cardiorespiratory coupling. The effect of ventilation on arterial pressure variations has significance to clinicians: such arterial pressure variation has been proposed as an index of adequate resuscitation.

Several methods have been proposed for assessment of the interdependences (e.g. synchronization) between signals following analysis of both experimental and simulated data. Three complementary approaches were employed: mutual coherence functions; phase synchronization indices; and entropy measures.

5. Summary of the most important results

Our data suggest that mechanical ventilation has substantial effects on at least one other organ system. These findings may be important in planning clinical strategies both to support the critically ill patient as well as to liberate critically ill patients from those supports, since the data imply that manipulation of ventilatory supports may propagate unanticipated and typically nonlinear effects to other organ systems.

We observed that mechanical ventilation entrains cardiovascular rhythms and increase cardio-respiratory synchronization. The resultant imposed dynamics of this multi-organ system is very different from the spontaneous dynamics of the healthy organism. Studies of cardio-respiratory synchronization in healthy young athletes demonstrated that “normal” synchronization lies between total “order” (full synchronization) and total “disorder” (no synchronization): the system slowly switches between regimes with different synchronization indices (n and m) through the periods of no synchronization. In most patients in this preliminary study, we found two extreme regimes: no synchronization during spontaneous respiration and full synchronization (“over-synchronization”) during mechanical ventilation. Possible effects of such prolonged over-synchronization on the functions of cardio-vascular-respiratory system are unknown. However, pathologic states have been attributed to oversynchronization within organs including the heart (reentrant arrhythmias) and brain (epilepsy can be defined as an abnormal synchronization in the brain).

Recently several studies, both theoretical and experimental have concluded that the noisy (or fractal) ventilation improves lung function in critical illness. The results of our study suggest that, due to coupling, biologically variable mechanical ventilation also may promote natural variability in other organ dynamics (e.g. in heart rate) and in organ-organ interactions (e.g. variable cardio-respiratory synchronization). This artificial “injection” of the variability may be beneficial for the critically ill patients since the decreased variability is usually associated with pathological states such as disease, including multiple organ dysfunction syndrome (MODS) and aging.

In this preliminary study we assessed the influence of mechanical ventilation of the lungs on the heart rate during clinical critical care: the modulation was assessed by coherence, the synchronization by phase dynamics, and irregularity by entropy. By comparing the results obtained using these methods we conclude that phase synchronization indices are the most sensitive measures cardio-respiratory interactions and they are most useful for discrimination between different regimes of cardio-respiratory dynamics (synchronization). We also found that, in critically ill patients, irregularity in respiration rate is not a (main) source of irregularity in heart rate. Finally, we conclude that new measures and displays of synchronization in the ICU could be useful to quantitatively assess interactions between organ systems.

6. Bibliography –N/A

7. Appendixes

Cardiorespiratory Dynamics during Transitions between Mechanical and Spontaneous Ventilation in Intensive Care

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Authorship Responsibilities: The two authors collaborated on all aspects of the report, including research design, data collection, analysis, manuscript preparation and editorial revision.

Key words: Mechanical Ventilation; Synchronization; Cardiopulmonary Interaction; Physiologic Variability; Homeostasis

Abstract

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We found that the mechanical ventilation not only drives lung dynamics but also affects the dynamics of cardiac and vascular systems. Spontaneous cardiovascular rhythms are entrained by the mechanical ventilator and are drawn into synchrony. Sudden interruption of mechanical ventilation typically leads to rapid desynchronization. This synchronization is restored upon reinstitution of mechanical ventilation.

The initial data suggest that therapies intended to support one organ system may propagate unanticipated effects to other organ systems. Moreover, sustained therapies may disturb mechanisms that promote natural synchronization and variability and thereby adversely affect recovery of normal organ system interactions. We suggest that new measures and displays of synchronization not only could provide insight into the organ-organ coupling but also could yield information to optimize the function of devices used to support the critically ill patient.

Introduction

Many organ systems exhibit oscillatory (cyclic) behavior. The period of the oscillations can be long (menstrual cycling, diurnal temperature variation); intermediate (glucose concentration have long [90 min] and short [3-7 min] oscillations; and short (respiratory and cardiac cycling). Organ systems are coupled with one another via mechanical, neural and other mechanisms. Thus, the organism as a whole (see [1] and references therein) - and respiratory and cardiovascular systems in particular (see e.g. [2]) - can be conceptually viewed as nested systems of coupled oscillators. From this perspective, a support device (here, the mechanical ventilator) acts as an external driving force on a biological oscillator (here, the lungs driven by the ventilator musculature). Since the lungs are coupled to other organ systems (e.g. heart and vessels), it might be expected that mechanical ventilation propagates its effects beyond the lungs to other organ systems and thereby modifies their dynamics.

Detecting the presence and strength of the influence of one organ's cycling upon others is technically challenging. Biological oscillators are noisy and their couplings are typically nonlinear. Moreover, it is important from both a clinical and a biophysical standpoint to ask how external forcing of one of the oscillators changes the dynamics of *other* "oscillators" (organs) and the interactions (e.g. synchronization) *among* them. Herein, we present preliminary results on the effect of the mechanical ventilation on cardiovascular dynamics and on cardiorespiratory[1] synchronization. The focus of this initial study is the simplest case of a driving force - mechanical ventilation with constant frequency and amplitude. (see Methods).

The lungs and the cardiovascular systems are known to be coupled by several mechanisms that promote modulation and synchronization. For example, parasympathetic (vagal) influences cause the

[1] In this paper, "ventilatory" and "respiratory" are taken to be synonomous. Although respiration technically refers to cellular processes involving oxidative phosphorylation and electron transport, historical terms such as "respiratory sinus arrhythmia" persist in common usage.

heart to beat faster during spontaneous inspiration and slower during exhalation. This phenomenon, which is called the respiratory sinus arrhythmia (RSA) [3], is thought beneficial for pulmonary gas exchange and circulatory efficiency [4]. From the point of view of physical theory of oscillation, RSA can be viewed as a frequency modulation of ECG by respiration. RSA is held responsible for high frequency (0.15-0.4 Hz) peak in the heart rate power spectra [5]. In addition to such modulations, another type of coupling has been recently described, namely the synchronization (locking) between instantaneous frequencies and phases of respiration and heartbeats [6,7]. A reciprocal influence (cardiac activity upon ventilatory dynamics) has also been recently described. Cardioventilatory coupling (CVC) has been suggested as a regulatory mechanism [8,9] separate from the RSA. The contribution of CVC is currently debated, since there appears to be near unidirectional interaction (i.e. lungs to heart) in human health after 6 months of age [10,11]. Regardless, there likely exists at least indirect and reciprocal coupling of cardiac activity upon ventilatory performance.

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Several methods have been proposed for assessment of the interdependences (e.g. synchronization) between signals following analysis of both experimental and simulated data (for the recent reviews see e.g. [12-14]). Three complementary approaches are used herein: mutual coherence functions; phase synchronization indices; and entropy measures.

Methods

Patient Selection

This observational study exploits a standard clinical practice - the spontaneous breathing trial (SBT). The SBT is a 30 minute period of spontaneous respiration preceded by and followed by respiration driven by a mechanical ventilator. The SBT is used as a screening procedure in order to assess the readiness of patients to be liberated from mechanical ventilatory support. The detailed description of the SBT procedure is given elsewhere (Partnership for Excellence in Critical Care. Multicenter Implementation of Evidence-Based Protocols: 1. Spontaneous Breathing Trials, in review at *Crit. Care Med.*). We studied 30 minute time intervals bracketing the SBT, together with the SBT time interval (Fig.1). This observational study was approved by the Washington University Human Research Protections Organization (WU-HRPO).

During the SBT the patients in our study were supported with constant (5 mmHg) continuous positive airway pressure (CPAP). Before and after the SBT, the patients were maintained on assist/control (A/C), where the ventilator creates positive air pressure waves at a given minimum frequency (usually 12 - 18 min^{-1} or equivalently, 0.2-0.3 Hz) with tidal volume set between 6 and 8 mL/kg. In this mode, patients are also capable of initiating breaths that are mechanically assisted with the full tidal volume.

The stated goal of this preliminary study is to investigate the transitions between mechanical ventilation and spontaneous breathing. Therefore we used a convenience sample of 13 patients (coded alphanumerically from P01 to P13) whose breathing rate during mechanical ventilation in assist-control mode was nearly constant at the set minimum frequency; whose breath volumes did not vary; whose clinical data streams were free of artifact; and who tolerated a 30 minute spontaneous breathing trial without adverse physiologic consequence. This selection allowed us to study the dynamics of multi-organ oscillatory system (lungs, heart and blood vessels) under the influence of external periodic driving force as well as transitions between periodically driven and free-running system.

Sedating drugs routinely prescribed to relieve patient anxiety were discontinued prior to the data collection. All patients were awake and responsive to complex commands ("raise two fingers") prior to beginning the SBT. We did not have data for the patient P12 following the SBT because he was extubated (disconnected from the ventilator) immediately after the SBT. The demographic data of all 13 patients are presented in Table 1. The diverse group consists of 7 males and 6 females with age range from 17 to 80 yr (46.08 ± 19.96 yr).

Data Collection

We used Philips IntelliVue™ M70 bedside monitors and Ixellence TrendFace™ software (http://www.ixellence.com) to continuously collect physiological waveforms, the duration of each of the three time intervals (before, during and after SBT) was 30 minutes. For all patients we recorded multi-channel ECG (at 500 Hz sampling frequency), end-tidal CO_2 (capnography) trace (at 62.5 Hz sampling frequency) as a respiratory signal, and the oxygen saturation (SaO_2) trace (at 125 Hz sampling frequency). Where available, we also recorded arterial blood pressure (ABP) and central venous pressure (CVP) traces (both at 125 Hz sampling rate). Within each 30 minute interval we

selected a 1000 sec (about 16.7 min) subinterval least contaminated by noise for further quantitative analysis.

Spectral Analysis

Power spectral analysis is a way to analyze periodicities in physiological signals [5,15]. Owing to the nonstationarity of the signals it is preferred to use a time-frequency representation in order to observe the frequencies of a signal and their change with time. Herein, we use a short-time Fourier transform (spectrogram) [16]. Using the spectral analysis of two signals (heart rate and respiration), we computed mutual coherence, which is a method of estimating the degree of the *linear* relationship between the signals:

$$C_{heart,resp}(f) = \frac{\left|P_{heart,resp}(f)\right|^2}{P_{heart}(f)\,P_{resp}(f)} \qquad (1)$$

$P_{heart}(f)$ and $P_{resp}(f)$ are the power spectral densities (psd) of the heart rate and respiratory signals respectively and $P_{heart,resp}(f)$ is cross-psd of the two signals. Mutual coherence ranges from zero (no coherence, two processes are linearly independent) to one (full coherence, two processes are linearly interrelated). We use here the value of the mutual coherence at the main respiratory frequency as a quantitative frequency-independent synchronization coefficient:

$$C_{h,r} = C_{heart,resp}(f_{resp}) \qquad (2)$$

The main respiratory frequency was defined as the frequency at which psd of the respiratory signal reaches its maximum. In almost all the cases the value (2) was also the maximum of the mutual coherence.

Prior to computation of power spectra and mutual coherence, all signals were re-sampled at the frequency of 4 Hz. Spectrograms and mutual coherences were calculated using Welch's averaged periodogram method [16].

Instantaneous Phase and Frequency Synchronization

In the case of weak coupling of two or more oscillatory processes, their phases can be synchronized (locked) while their amplitudes may be completely uncorrelated [17]. Relative phase dynamics also can capture nonlinear interactions between the systems under investigation. Thus study of phase dynamics can reveal synchronization even when it is undetectable using linear spectroscopic techniques (as in the prior section). In this section, we describe methods we used to extract phase dynamics from ECG and respiratory signals and to quantify the degree of phase synchronization between heart and lung "oscillators".

Phase

The most formal way of obtaining phase dynamics $\varphi(t)$ from a signal dynamics *x(t)* is to perform Hilbert Transform of the signal (see [17,18]):

$$x_H(t) = \frac{1}{\pi} P.V. \int_{-\infty}^{\infty} \frac{x(\tau)}{t-\tau} d\tau \qquad (3)$$

(here P.V. means that the integral is taken in the sense of the Cauchy principal value) and construct the analytical signal:

$$\varsigma(t) = x(t) + i x_H(t) = A(t)\exp(i\varphi(t)) \qquad (4)$$

This gives the Hilbert phase:

$$\varphi(t) = \arctan\left(\frac{x_H(t)}{x(t)}\right) \qquad (5)$$

and instantaneous frequency:

$$f(t) = \frac{d\varphi(t)}{dt} \qquad (6)$$

An alternate and simpler approach is based on Poincare section [6,17]. Practically, we collected all time moments t_n when a signal crosses some threshold level in one direction (e.g. from below to above) and then attributed a phase increase of 2π (one cycle) to each crossing point (see also [19]). This simpler method is illustrated in Fig.2 for ECG and capnography signals. For ECG signal Poincare section method is reduced to finding times of R peaks on electrocardiogram and then attributing them to t_n. Then we used piecewise linear interpolation to define instantaneous phases for ECG and respiration over whole time interval:

$$\varphi_{heart}(t) = 2\pi \frac{t - t_n^{heart}}{t_{n+1}^{heart} - t_n^{heart}} + 2\pi n \qquad t_n^{heart} \le t < t_{n+1}^{heart} \tag{7}$$

$$\varphi_{resp}(t) = 2\pi \frac{t - t_n^{resp}}{t_{n+1}^{resp} - t_n^{resp}} + 2\pi n \qquad t_n^{resp} \le t < t_{n+1}^{resp} \tag{8}$$

The instantaneous frequency was defined as

$$f_n = 1/(t_{n+1} - t_n) \tag{9}$$

and set constant within one cycle. We selected this definition of the instantaneous frequency over the formal definition (6) since the Hilbert Transform can result not only in large fluctuations but even in negative values of frequency [20]. Moreover, the frequency definition (9) is more consistent with the physiological and clinical definitions of heart (or respiration) rate as inverse beat-to-beat (breath-to-breath) interval.

Phase Synchronization

Phase synchronization is usually defined [20] as locking (or entrainment) of two phases such that the generalized phase difference

$$\varphi_{n,m}(t) = n\varphi_{heart}(t) - m\varphi_{resp}(t) \tag{10}$$

(where *m* and *n* are integers) remains constant. In practice, due to the external or the internal "noise", the phase difference (10) fluctuates around some constant value. We therefore use the following condition as the definition of (*n:m*) phase synchronization:

$$\left| n\varphi_{heart}(t) - m\varphi_{resp}(t) - \delta \right| < \varepsilon \qquad (11)$$

where the amplitude of fluctuations, ε, must be less than 2π. Fluctuations (e.g. extra heartbeats per respiratory cycle) can also cause so-called "phase slips" i.e. a rapid jump of $\varphi_{n,m}$ by $\pm 2\pi k$ resulting in a physically equivalent state (due to cyclic 2π periodicity of the phase). Thus in the presence of noise, the condition (11) may be valid only "piecewise".

One way to visually detect the phase synchronization is to use the "stroboscopic" approach, namely to observe a phase of a "slower" signal (in this case, respiration) at times when the cyclic phase of the "fast" signal (ECG) reaches a certain fixed value, e.g. 0 or 2π (that is, at the time of R peak in the ECG, according to the phase definition (7)). The sequence of such observations (values of phase of respiration at times of R peaks in ECG) is termed the "synchrogram" [20]:

$$\psi_m(t) = \frac{1}{2\pi}\left[\varphi_{resp}(t_n^{heart}) \bmod 2\pi m \right] \qquad (12)$$

When plotted as a function of time, the synchrogram shows how many of heartbeats accrue during *m* respiratory cycles. Horizontal strips on the synchrogram indicate *n:m* synchronization (where *n* is the number of strips) namely constant number of *n* heartbeats per *m* respiratory cycles [6].

Synchronization Indices

Several indices have been proposed to quantitatively measure phase synchronization [20]. We employed two that are based on the analysis of *cyclic* generalized phase difference:

$$\psi_{n,m}(t) = \varphi_{n,m}(t) \bmod 2\pi \qquad (13)$$

The first index $\rho_{n,m}$ is based on the Shannon entropy of the generalized phase difference distribution:

$$\rho_{n,m} = \frac{S_{\max} - S}{S_{\max}} \qquad (14)$$

Where $S = -\sum_{k=1}^{N} p_k \ln p_k$ (the entropy of the histogram of $\psi_{n,m}$) and the maximum entropy is given by $S_{\max} = \ln N$. N is the number of bins and p_k is the probability of finding $\psi_{n,m}$ within the k^{th} bin. The optimal number of bins can be estimated as $N = \exp[0.626 + 0.4\ln(M-1)]$ where M is number of samples [21].

The second index is the intensity of the first Fourier mode of the phase difference distribution:

$$\gamma_{n,m} = \sqrt{\left|\left\langle \exp(i\psi_{n,m}(t))\right\rangle\right|} = \sqrt{\left\langle \cos(\psi_{n,m}(t))\right\rangle^2 + \left\langle \sin(\psi_{n,m}(t))\right\rangle^2} \qquad (15)$$

where the brackets denote the average over time. Both indices vary from 0 (no synchronization) to 1 (full synchronization).

For periodic oscillators the condition of phase locking (10) is equivalent to the condition of frequency locking:

$$\alpha = \frac{f_{heart}}{f_{resp}} = \frac{n}{m} \qquad (16)$$

where f_{resp} and f_{heart} are instantaneous frequencies defined by (9). However in more complex cases (e.g. in the presence of noise or in the case of chaotic oscillations) these conditions are not equivalent, so that frequency locking may exist without phase locking or the opposite [7]. Thus one must check both conditions (11) and (16) while searching for cardiorespiratory synchronization.

The dynamics of two coupled phase oscillators can be conveniently visualized as a trajectory on a torus (see e.g. [22]). In the case of frequency locking (16) all trajectories are closed orbits on the torus and the motion is periodic. Such a torus is often called resonant or rational. Alteratively, when the frequency ratio (16) is irrational, the trajectories cover whole torus (they never intersect and never close) and the motion is quasi-periodic. This torus is referred to as ergodic or irrational.

Note that both indices of phase synchronization (14) and (15) are functions of *n* and *m*, so both integers must be determined before using the indices. This can be done by finding the integers that produce constant phase difference (11) or frequency ratio (16) or as the ratio of the main peak frequencies in power spectra of heart rate and respiration. Also, both integers n and m must be relatively small since any (even irrational) value of α (16) can be approximated (within any given accuracy) using large enough integers (see e.g. [23] for the discussion).

Entropy

We used entropy measures in order to quantify the irregularity of both cardiac and respiratory signals. Entropy measures are widely used for the analysis of physiological signals because they can be applied to relatively short, noisy and non-stationary signals. Entropy also captures some non-linear properties of a signal.

We used two estimators of the entropy, namely, approximate entropy (ApEn) [24] and sample entropy (SampEn) [25]. Both estimators measure the repetition of patterns within a given signal. They are related to the conditional probability that two sequences that are similar for *m* points remain similar (within a tolerance *r*) at the next point, except that in the case of the sample entropy self-matches are excluded. Because of this property, sample entropy is believed to be a better estimator [26,27].

We constructed a sequence of inter-beat intervals for each of two signals:

$$RR_n = t_{n+1}^{heart} - t_n^{heart} \text{ and } BB_n = t_{n+1}^{resp} - t_n^{resp}, \qquad (17)$$

and then calculated two estimators of the entropy using the following formulas ([27]):

$$ApEn(m,r,N) \approx \frac{1}{N-m}\sum_{i=1}^{N-m}\ln\frac{l_i^m}{l_i^{m+1}} \quad (18)$$

$$SampEn(m,r,N) = \ln\frac{\sum_{i=1}^{N-m} l_i'^m}{\sum_{i=1}^{N-m} l_i'^{m+1}} \quad (19)$$

where l_i^m and l_i^{m+1} are numbers of sub-sequences or "patterns" (of length m and m+1 points respectively) that are close to each other (within a tolerance *r*), N is the number of inter-beat intervals. *l'* designates the number of sequences when self-matches are not counted. We used tolerance *r=0.2* SD (that is, 20% of the standard deviation of the data) and pattern length *m=2* for both heart and respiratory rates analysis.

Data Analysis Details

KubiosHRV^{TM} software [28] was used to extract heart rate intervals (RR intervals) from single-lead 500 Hz ECG signals. We used MATLAB code from the Physionet website (www.physionet.org) [29] for our calculations of the sample entropy. The rest of the signal analysis was done with custom written code and standard functions of the MATLAB programming environment (www.mathworks.com). Statistical analysis was also performed within MATLAB using paired t-test.

Results

Spectral Analysis

Heart rate

During mechanical ventilation (before and after the SBT) the power spectra of the respiratory signal had the expected single very sharp peak at the constant frequency of mechanical ventilator. Due

to RSA the power spectra of the heart rate also had a sharp peak (the so-called high frequency peak) at the frequency of ventilator (Fig.3). During the period of spontaneous respiration (SBT) the peak on respiration power spectra was smaller and much wider reflecting more natural respiration variability. The high frequency peak on the heart rate power spectra followed the evolution of the respiratory peak (and in some cases the high frequency peak almost [but never completely] disappeared during the spontaneous respiration). Both peaks reappeared after the mechanical ventilation was reapplied. This results shows that there is a strong modulation of the heart rate by respiration.

The linear coupling between respiration and heart rate signals were estimated using the mutual coherence function (1). In Fig. 3, we present respiration and heart rate power spectra together with the mutual coherence for one of the patients (P02), before, during and after the SBT. In order to quantify the degree of linear coupling, we calculated the values of the cardio-respiratory coherence at the main respiratory frequency (2) for all 13 patients before, during and after SBT. The results are presented on Fig. 4 and in Table 2. We did not observe any statistically significant difference in the degree of linear coupling during the SBT compared to the bracketing intervals of mechanical ventilation. The coupling was relatively strong regardless of the regime of the respiration (mechanical/periodic vs. spontaneous/variable).

Vascular rhythms

As previously noted, ventilation modulates vascular rhythms in two independent ways: frequency modulation (due to RSA) and baseline modulation (due to pressure variation in the thoracic cavity). Examples of these two types of modulation are shown on Fig.5 which are illustrated for two patients, the first one (P02, the same as on Fig.3) with strong RSA (heart rate changes in phase with respiration (CO_2) signal) and the second one (P04) with rather weak RSA (heart rate has mostly low frequency oscillations). Both patients however have baseline (local maxima and minima) modulation

of all their vascular rhythms (arterial and central venous blood pressure and oxygen saturation). In fact, the modulation of the vascular rhythms in the patient with weak RSA was even stronger. These examples show that the ventilator can entrain the vascular rhythms even in the absence of RSA or any cardio-respiratory synchronization. The modulation can be visualized using spectral analysis. The spectrograms (time-frequency power spectra representations) of the respiration (CO_2), heart rate, arterial blood pressure, central venous pressure and oxygen saturation signals for the patient P04 during a 1h 50 min time interval are presented on Fig.6. The spectrograms demonstrate that all cardiovascular rhythms are entrained and follow the rhythm of respiration. In particular, during periodic mechanical ventilation all vascular rhythms lose their natural variability and also become periodic. In each of the 13 patients, we observed that mechanical ventilation entrains both cardiac and vascular rhythms in a way similar to the effect of paced respiration (see e.g. [30]). In this preliminary study we did not attempt to further quantify the degree of vascular-respiratory modulation.

Phase and Frequency Synchronization

We found that the respiratory and cardiac frequencies and phases are more synchronized during the mechanical ventilation compare to the spontaneous breathing. Thus the effect of almost periodic mechanical ventilation on cardio-respiratory synchronization is similar to effect of paced respiration (see e.g. [19]). In several cases we observed full synchronization (both phase and frequency locking) with fixed locking indices n and m during the whole interval of the mechanical ventilation. An example of such a full synchronization (patient P09) is presented in Fig.7. Initially (before the trial) both phase and frequency locking exists with 1:5 locking indices. Note, that both respiratory and cardiac instantaneous frequencies decrease, but their ratio α remains constant (Fig.8a) which indicates perfect frequency locking. The synchrogram ψ_2 shows ten horizontal strips (equivalently, its distribution has 10 peaks) which again corresponds to 1:5 (2:10) locking. Sudden interruption of

mechanical ventilation causes full desynchronization (see also Fig.8b), which is restored by reinstitution of mechanical ventilation. Note that the desynchronization occurs very quickly while the resynchronization requires much longer time, since it takes time for the system to be entrained by the external force (mechanical ventilator). After the mechanical ventilator was turned on again (at about 4520sec) initially very short windows of synchronization appeared (the first one is in between 4750 sec and 5000 sec and the second one is around 5250 sec), eventually a long (5700-6500 sec) time interval of phase and frequency 1:5 synchronization occurs (presented also in Fig.8b) and finally the dynamics stabilizes in fully synchronized state with 1:4 locking for both phase and frequency.

Locking indices n and m (needed for the definition of the generalized phase differences $\varphi_{n,m}$ (10) and for the calculation of synchronization indices $\rho_{n,m}$ (14) and $\gamma_{n,m}$ (15)) can be determined from the number of horizontal strips on the synchrogram ψ_2, if such strips exist (see e.g. Fig.8a and Fig.8c). In case when no phase or frequency synchronized is detectable (that is the synchrogram does not have horizontal strips and frequency ratio is not constant) which was the typical situation for SBT time intervals (see e.g. Fig.8b) they still can formally be calculated from the maxima of the distribution of the frequencies ratio, α. In this case (see Fig.8b) calculation yields 1:8 coupling during the SBT.

Generalized phase differences $\varphi_{n,m}$ together with their cyclic probability distribution (for the same three time intervals as on Fig.8) are shown on Fig.9. Note that strong fluctuations (spikes) of respiratory frequency f_{resp} (due to spontaneous respiration of the patient) at about 20 sec. and 350 sec. (Fig. 8a) cause spikes in α and phase slips in the phase difference $\varphi_{1,5}$ (Fig. 9, top). The time interval after the SBT (Fig. 8c) contains even more spikes in f_{resp} which leads to large number of phase slips (Fig. 9, bottom). These fluctuations however do not disrupt the synchronization in the statistical sense.

It is instructive to compare phase difference trajectories during and after SBT ($\varphi_{1,8}$ and $\varphi_{1,5}$, respectively, see Fig.9). Although the fluctuations of $\varphi_{1,8}$ and $\varphi_{1,5}$ look similar, their cyclic distributions (that are not sensitive to 2π phase slips) $\psi_{1,8}$ and $\psi_{1,5}$ (Fig.9, right column) are distinctly different allowing separation of unsynchronized (uniform distribution) and synchronized (distribution with a sharp peak) regimes [20]. These distributions are used in calculation of the entropy-based synchronization index $\rho_{n,m}$ (15).

Another method for qualitative separation between synchronous and asynchronous phase oscillations is presented on Fig.10. The figure shows the cardio-respiratory phase dynamics as trajectory on a torus (top) and 2D distribution of respiratory and cardiac phases for the same three sub-intervals (as on Figs. 8 and 9): before (a), during (b) and after (c) the SBT. During the mechanical ventilation (before and after) the phases are distributed in the ordered way (1:5 linear dependence between phases) which corresponds to the resonant tori with periodic orbits. During the spontaneous respiration the phases are distributed uniformly (no dependence is detectably from the 2D histogram) which corresponds to the ergodic torus (the trajectory covers whole torus).

Not all 13 patients demonstrated such perfect synchronization (both phase and frequency locking) during periodic mechanical ventilation. As an example, a 45 min (2750 sec) time interval of periodic ventilation (before the SBT) is presented on Fig.11 (patient P10). Respiratory frequency f_{resp} remains constant and the cardiac frequency f_{heart} and the frequency ratio α fluctuate in a narrow intervals (see the corresponding distributions). Yet, no phase synchronization is detectable from the synchrogram (in particular its distribution is uniform). This result is similar to the result obtained by [2] for the (mechanically ventilated) critically ill patient in coma. [2] showed that in this case both

respiratory and cardiac frequencies are constant (resulting in constant frequency ratio) but no phase synchronization is detectable. Based on this observation they concluded that the two systems are uncoupled. Here, these two systems cannot be considered to be "uncoupled" since (for example) strong mutual coherence exists between the respiratory and heart rate signals (see Table 2).

In this case, the locking indices m and n can still be formally determined from the frequency ratio distribution (in the same way as for the SBT time intervals). It has a relatively sharp maximum at $\alpha \approx 7.75$ which gives n:m=31:4 locking (15). Note that even such a formal introduction of the locking indices (without any detectable phase synchronization) leads to higher values of phase synchronization indices (both $\rho_{n,m}$ and $\gamma_{n,m}$) for the periodic ventilation compare to the spontaneous breathing (see Table 2 for the results for the patient P10). It means that some (even visually undetectable) coupling between phases still exists and thus different indices are needed for the synchronization assessment. Mutual information could be a good candidate, since locking indices n and m are not required for its calculation [31].

The values of two indices of phase synchronization: $\gamma_{n,m}$ (14) and $\rho_{n,m}$ (15) for all 13 patients before, during and after the SBT are given on Table 2 and Fig.12. There is a statistically significant difference between synchronization indices during spontaneous respiration compare to the mechanical ventilation. We also found high correlation (correlation coefficient R=0.9-0.96, $p<10^{-4}$) between the two phase synchronization indices ($\gamma_{n,m}$ and $\rho_{n,m}$) for all 3 time intervals (before, during and after SBT).

Finally, we are unaware of any measure (or index) of the degree of *instantaneous* frequency synchronization and thus it was not quantified in this paper. Without such a metric, it could be possible

to fail to detect cardiorespiratory synchronization because (as we mentioned earlier, see Fig.11) such synchronization could exist even in the absence of phase locking. Regimes of cardiorespiratory dynamics with frequency locking but without phase locking have been found in [32].

Entropy

The results of the entropy analysis of heart and respiration rates are presented on Table 3 and Figs.13 and 14. As expected, we found that the respiration rate entropies (both ApEn and SampEn) increase during the SBT since the spontaneous respiration is more irregular then almost periodic respiration driven by mechanical ventilator. However, we did not find any statistically significant change in both ApEn and SampEn of the heart rate during the SBT compare to periods of mechanical ventilation. Moreover, within each of the three time intervals studied (before, during and after the SBT) we found no *linear* correlation between the entropy (that is, irregularity) of respiration rate and entropy of heart rate (Fig. 14), except maybe in case of sample entropies of respiration and heart rates before the SBT ($p=0.0725$). We did not estimate any *nonlinear* correlation coefficient.

Based on the coupled oscillator hypothesis, we would expect that the entropy of heart rate should increase as the entropy of the respiration rate increases (because of almost unidirectional coupling between the lung and the heart [33]**,** see however [9]). We cannot however conclude that two systems are uncoupled because of strong modulation of the hart rate by respiration (RSA, see Table 2). Also the interactions between the two systems are somewhat different during spontaneous and mechanical ventilation, since in the latter case the systems are more synchronized in terms of their phase dynamics (Table 2). Since the entropy is a way of measuring nonlinear properties of the signal, our results are consistent with the previous finding of [34] that the nonlinearity of respiration is not the origin of nonlinearities in heart rate. [34] compared other measures of heart rate nonlinearity

(correlation dimension and nonlinear predictability) during spontaneous and paced respiration in healthy subjects and did not find any difference between these two regimes.

We found high correlation (correlation coefficient R=0.96-0.98, $p<10^{-4}$) between the two entropy estimators for all 3 time intervals (before, during and after SBT).

Discussion

This initial study has several important limitations. First, it is an observational study of a convenience sample in which the SBT was the only consistent perturbation. Second, the initial study population is deliberately inhomogeneous with respect to age, gender, ethnicity and indication for ICU admission. Third, this initial study group is very small (13 patients) owing to the number and complexity of the analyses. Although the study shows complex interactions between the respiratory and cardiovascular systems, neither heritable (genetic) contributions, nor the contributions of chronic illness, nor the contributions of the illness that precipitated ICU admission, nor the contributions of any other drug treatment or therapy can be identified in this initial study. Despite these limitations, the study provides insight not only into the complexity of the interactions but also into the profound effects of mechanical ventilatory support beyond the lungs.

The data suggest that mechanical ventilation has substantial effects on at least one other organ system. These findings may be important in planning clinical strategies both to support the critically ill patient as well as to liberate critically ill patients from those supports, since the data imply that manipulation of ventilatory supports may propagate unanticipated and typically nonlinear effects to other organ systems.

We observed that mechanical ventilation entrains cardiovascular rhythms and increase cardio-respiratory synchronization. The resultant imposed dynamics of this multi-organ system is very different from the spontaneous dynamics of the healthy organism. Studies of cardio-respiratory synchronization in healthy young athletes [6] demonstrated that "normal" synchronization lies between total "order" (full synchronization) and total "disorder" (no synchronization): the system slowly switches between regimes with different synchronization indices (n and m) through the periods of no synchronization. In most patients in this preliminary study, we found two extreme regimes: no synchronization during spontaneous respiration and full synchronization ("over-synchronization") during mechanical ventilation. Possible effects of such prolonged over-synchronization on the functions of cardio-vascular-respiratory system are unknown. However, pathologic states have been attributed to oversynchronization within organs including the heart (reentrant arrhythmias) and brain (epilepsy can be defined as an abnormal synchronization in the brain [14]).

Recently several studies, both theoretical [35,36] and experimental [37-39] have concluded that the noisy (or fractal) ventilation improves lung function in critical illness. The results of our study suggest that, due to coupling, biologically variable mechanical ventilation also may promote natural variability in other organ dynamics (e.g. in heart rate) and in organ-organ interactions (e.g. variable cardio-respiratory synchronization). This artificial "injection" of the variability may be beneficial for the critically ill patients since the decreased variability is usually associated with pathological states such as disease, including multiple organ dysfunction syndrome (MODS)[1,40,41] and aging [42].

In this preliminary study we assessed the influence of mechanical ventilation of the lungs on the heart rate during clinical critical care: the modulation was assessed by coherence, the synchronization by phase dynamics, and irregularity by entropy. By comparing the results obtained using these methods we conclude that phase synchronization indices are the most sensitive measures cardio-respiratory interactions and they are most useful for discrimination between different regimes of

cardio-respiratory dynamics (synchronization). We also found that, in critically ill patients, irregularity in respiration rate is not a (main) source of irregularity in heart rate. Finally, we conclude that new measures and displays of synchronization in the ICU could be useful to quantitatively assess interactions between organ systems.

Supplementary Material

A movie file (13.4 MB) with the animation of the top part of the Fig. 10 is available at the following URL: www.burykin.com/torus.avi. It visualizes the dynamics of cardiac and respiratory phases as a trajectory on a torus during 2 hours time interval which includes both mechanical and spontaneous respiration as well as transitions between these two regimes.

Figure Legends.

1. Schematic representation of the air pressure P(t) created by the mechanical ventilator, as a function of time during the time interval used in the study. The time interval consists of approximately 30 minute period of spontaneous respiration (indicated as "SBT" on the figure) preceded and followed by two 30 minute periods of respiration driven by mechanical ventilator (indicated as "BEFORE" and "AFTER", respectively). During the SBT the ventilator provides small constant positive pressure. Before and after the SBT the ventilator creates positive pressure waves with a given constant period τ (they are drawn by solid rectangular pulses along the time axis). It also supports spontaneous breathing if the patient initiates a breath (drawn as dashed rectangular pulses). For this initial study we selected only patients with no or very small spontaneous respiration rate. The gray arrows with "off (on)" labels indicate time moments when the periodic force is withdrawn (reapplied).

2. Illustration of the phase definition method using Eq.7 and Eq.8 for respiratory (top) and cardiac (bottom) signals. Horizontal dashed lines indicate the chosen threshold levels.

3. Power spectral densities (calculated by Welch averaging method) of the respiratory (CO_2) (1^{st} row) and heart rate (HR) (2^{nd} row) signals and cardio-respiratory coherence (3^{rd} row) of the patient P02 for three 1000 sec. time intervals: before (1^{st} column), during (2^{nd} column) and after (3^{rd} column) SBT.

4. Values of the cardio-respiratory coherence at the main respiratory frequency (Eq.2) for 13 patients for three 1000 sec. time intervals: before, during and after SBT (p values were determined using paired t-tests). See also Table 2.

5. Respiratory (CO_2), heart rate (HR), arterial blood pressure (ABP), central venous pressure (CVP) and oxygen saturation (SaO_2) signals for the patients P02 (left panel) and P04 (right panel) during 7 respiratory cycles intervals (periodic mechanical ventilation regime). In the case of patient P02 both frequency and baseline modulation of the vascular signals are present. Patient P04 has very weak RSA (and thus no frequency modulation of the vascular rhythms by respiration). However even in the absence of RSA there is a baseline modulation of the vascular oscillations by respiration (by the ventilator) which is even stronger than in the case of patient P04.

6. Spectrograms of respiratory (CO_2), heart rate (HR), arterial blood pressure (ABP), central venous pressure (CVP) and oxygen saturation (SaO_2) signals for the patient P04 during 1h50min time interval (before, during and after the SBT). Arrows on the time axis indicate the beginning and the end of SBT.

7. Instantaneous respiration (a) and heart (b) frequencies (Eq.9), their ratio α (Eq.16) (c) and phase synchrogram ψ_2 (Eq.12) (d) for the 2 hour time interval (before, during and after the SBT) for the patient P09. Arrows on the time axis (at the bottom) indicate the beginning and the end of SBT.

8. Three sub-intervals from the Fig.7: before (a), during (b) and after (c) the SBT. The right-hand column shows the corresponding distributions.

9. Generalized phase difference $\varphi_{n,m}$ (Eq.10) and its cyclic distribution $\psi_{n,m}$ (Eq.13) for the same three sub-intervals as on Fig.7: before (a), during (b) and after (c) the SBT. Locking indices n and m were determined from the number of horizontal strips on the synchrogram ψ_2 (cases (a) and (c)) or from the maxima of the distribution of the frequencies ratio α (case (b)) (see Fig.8).

10. Representation of the cardio-respiratory phase dynamics as trajectory on a torus (top) and 2D distribution of respiratory and cardiac phases (bottom) for the same three sub-intervals as on Figs.8 and 9: before (a), during (b) and after (c) the SBT.

11. Instantaneous respiration (a) and heart (b) frequencies (Eq.9), their ratio (c) α (Eq.16) and phase synchrogram (d) ψ_2 (Eq.12) for the 45 min (2750 sec) time interval of mechanical ventilation (before SBT) for the patient P10. The left-hand column shows the corresponding distributions.

12. Two indices of cardio-respiratory phase synchronization: $\gamma_{n,m}$ (Eq.14) and $\rho_{n,m}$ (Eq.15) for 13 patients before, during and after SBT (p values were determined using paired t-tests). See also Table 2.

13. Approximate and sample entropies of heart rate and respiration rate (HR and RR, upper and lower parts, respectively) for 13 patients before, during and after SBT (p values were determined using paired t-tests). See also Table 3.

14. Scatter plots and coefficients of cross-correlation between approximate and sample entropies of heart rate (HR) and respiration rate (RR) for 13 patients before, during and after SBT.

Table 1. Demographics summary for the patients included in the study

Patient	Age	Gender
P01	36	Male
P02	61	Male
P03	52	Male
P04	45	Female
P05	17	Female
P06	69	Male
P07	71	Female
P08	23	Male
P09	52	Female
P10	34	Female
P11	32	Female
P12	80	Male
P13	27	Male

Table 2. Locking indices n:m (Eq.9), mutual coherence $C_{h,r}$ (Eq.2) and two indices of phase synchronization $\gamma_{n,m}$ (Eq.14) and $\rho_{n,m}$ (Eq.15) before, during and after SBT.

Patient	***n:m***			$C_{h,r}$			$\rho_{n,m}$			$\gamma_{n,m}$		
	BEFORE	**SBT**	**AFTER**	**BEFORE**	**SBT**	**AFTER**	**BEFORE**	**SBT**	**AFTER**	**BEFORE**	**SBT**	**AFTER**
P01	1:7	1:4	1:7	0.97	0.86	0.96	0.024	0.0018	0.0241	0.2375	0.0574	0.2247
P02	1:5	2:15	1:5	0.99	0.83	0.99	0.0027	7.82e-04	0.0102	0.0515	0.0093	0.1646
P03	1:5	2:9	4:21	0.75	1	0.82	0.0348	0.0053	0.0039	0.1337	0.1156	0.0855
P04	1:6	1:9	1:7	0.9	0.22	0.93	0.0057	7.21e-04	0.0032	0.1186	0.036	0.051
P05	4:23	1:11	1:7	0.95	0.75	0.98	0.0051	0.0016	0.0316	0.0581	0.026	0.3223
P06	4:25	2:13	3:19	0.95	0.85	0.98	0.0033	6.83e-04	0.0058	0.0139	0.0232	0.0949
P07	2:15	1:9	2:17	0.83	0.64	0.64	0.0074	8.14e-04	0.0035	0.1085	0.0505	0.0611
P08	1:4	2:7	1:4	0.28	0.95	0.97	0.3961	6.28e-04	0.1219	0.9572	0.0267	0.6231
P09	1:5	1:8	1:5	1	0.96	0.97	0.2771	0.0013	0.0716	0.9073	0.0367	0.5198
P10	4:31	2:9	1:8	0.96	0.9	0.88	0.0062	4.04e-04	0.0627	0.1081	0.0221	0.4212
P11	1:9	1:6	1:9	0.9	0.94	0.84	0.0099	6.36e-04	0.0062	0.0572	0.0277	0.1524
P12	1:4	2:9	no data	0.78	0.65	no data	0.411	7.61e-04	no data	0.9762	0.0328	no data
P13	1:5	1:3	1:3	0.81	0.68	0.98	0.0359	8.59E-04	0.0404	0.3925	0.0405	0.4311
mean				*0.8515*	*0.7869*	*0.9117*	*0.0938*	*0.0013*	*0.0321*	*0.3169*	*0.0388*	*0.2626*
SD				*0.1830*	*0.2007*	*0.0991*	*0.1498*	*0.0012*	*0.0353*	*0.3575*	*0.0252*	*0.1874*

Table 3. Approximate (ApEn) and sample (SampEn) entropies for heart rate (HR) and respiration rate (RR) before, during and after SBT.

Patient	**HR**						**RR**					
	ApEn			**SampEn**			**ApEn**			**SampEn**		
	BEFORE	**SBT**	**AFTER**	**BEFORE**	**SBT**	**AFTER**	**BEFORE**	**SBT**	**AFTER**	**BEFORE**	**SBT**	**AFTER**
P01	0.6554	0.7853	0.7022	0.3918	0.5247	0.4294	1.0531	1.3189	1.2825	0.7334	0.9154	0.9039
P02	1.1261	1.8049	1.822	0.8417	1.4966	1.4733	0.3893	1.8703	0.5509	0.1907	1.9795	0.2989
P03	1.8202	2.1949	0.3912	1.4817	2.1255	0.298	1.2749	1.8143	0.5155	1.2553	1.9036	0.6554
P04	1.5084	1.092	1.2051	1.2331	0.7842	0.9777	1.9917	1.7546	0.3511	2.1132	2.0543	0.1307
P05	1.8002	0.4676	0.6986	1.5185	0.2773	0.4364	1.9221	1.8859	0.9704	1.9009	1.9401	0.6603
P06	1.7193	1.9214	1.6496	1.2487	1.5911	1.1616	1.0598	1.9503	0.4795	1.0704	2.2908	0.1929
P07	1.49	0.926	0.9583	1.0216	0.5836	0.6367	0.2271	1.9023	0.5296	0.053	1.8563	0.1479
P08	1.3201	0.3913	0.3332	1.0617	0.2282	0.1957	1.2589	1.695	1.1291	1.0398	1.4876	0.4648
P09	1.6822	1.8081	1.174	1.6462	1.432	0.9715	0.7511	1.7848	1.0226	0.6166	1.7384	0.6126
P10	1.8907	1.3758	1.5339	1.4552	1.0119	1.0065	1.6918	1.8375	1.1704	1.7723	1.722	0.8648
P11	0.7244	1.2803	1.6265	0.4406	0.9652	1.212	1.3445	1.9704	1.3032	0.6782	1.8377	0.8842
P12	1.976	1.0559	no data	1.728	0.6927	no data	1.7175	1.939	no data	1.5886	1.9908	no data
P13	1.4912	1.1266	1.9293	1.0724	0.8699	1.6645	1.433	1.2078	2.0561	1.2705	0.725	2.0025
mean	*1.4772*	*1.2485*	*1.1687*	*1.1647*	*0.9679*	*0.8719*	*1.2396*	*1.7639*	*0.9467*	*1.0987*	*1.7263*	*0.6516*
SD	*0.4051*	*0.5355*	*0.5296*	*0.4054*	*0.5344*	*0.4524*	*0.5239*	*0.2277*	*0.4699*	*0.6130*	*0.4282*	*0.4903*

References

1. Godin, P. J.; Buchman, T. G. Uncoupling of biological oscillators: A complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Critical Care Medicine 1996, 24, 1107-1116.

2. Stefanovska, A.; Lotric, M. B.; Strle, S.; Haken, H. The cardiovascular system as coupled oscillators? Physiological Measurement 2001, 22, 535-550.

3. Hales, S. Essay II, Haemastaticks. Innings Manby: London, 1733.

4. Hayano, J.; Yasuma, F.; Okada, A.; Mukai, S.; Fujinami, T. Respiratory sinus arrhythmia - Phenomenon improving pulmonary gas exchange and circulatory efficiency. Circulation 1996, 94, 842-847.

5. Akselrod, S.; Gordon, D.; Ubel, F. A.; Shannon, D. C.; Berger, A. C.; Cohen, R. J. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981, 213, 220-222.

6. Schafer, C.; Rosenblum, M. G.; Kurths, J.; Abel, H. H. Heartbeat synchronized with ventilation. Nature 1998, 392, 239-240.

7. Schafer, C.; Rosenblum, M. G.; Abel, H. H.; Kurths, J. Synchronization in the human cardiorespiratory system. Physical Review E 1999, 60, 857-870.

8. Galletly, D. C.; Larsen, P. D. Relationship between cardioventilatory coupling and respiratory sinus arrhythmia. British Journal of Anaesthesia 1998, 80, 164-168.

9. McGuinness, M.; Hong, Y.; Galletly, D.; Larsen, P. Arnold tongues in human cardiorespiratory systems. Chaos 2004, 14, 1-6.

10. Rosenblum, M. G.; Cimponeriu, L.; Bezerianos, A.; Patzak, A.; Mrowka, R. Identification of coupling direction: Application to cardiorespiratory interaction. Physical Review E 2002, 65, -.

11. Mrowka, R.; Cimponeriu, L.; Patzak, A.; Rosenblum, M. G. Directionality of coupling of physiological subsystems: age-related changes of cardiorespiratory interaction during different sleep stages in babies. American Journal of Physiology-Regulatory Integrative and Comparative Physiology 2003, 285, R1395-R1401.

12. Quiroga, R. Q.; Kraskov, A.; Kreuz, T.; Grassberger, P. Performance of different synchronization measures in real data: A case study on electroencephalographic signals. Physical Review E 2002, 65, -.

13. Kreuz, T.; Mormann, F.; Andrzejak, R. G.; Kraskov, A.; Lehnertz, K.; Grassberger, P. Measuring synchronization in coupled model systems: A comparison of different approaches. Physica D: Nonlinear Phenomena 2007, 225, 29-42.

14. Pereda, E.; Quiroga, R. Q.; Bhattacharya, J. Nonlinear multivariate analysis of neurophysiological signals. Progress in Neurobiology 2005, 77, 1-37.

15. Camm, A. J.; Malik, M.; Bigger, J. T.; Breithardt, G.; Cerutti, S.; Cohen, R. J.; Coumel, P.; Fallen, E. L.; Kennedy, H. L.; Kleiger, R. E.; Lombardi, F.; Malliani, A.; Moss, A. J.; Rottman, J. N.; Schmidt, G.; Schwartz, P. J.; Singer, D. Heart rate variability - Standards of measurement, physiological interpretation, and clinical use. Circulation 1996, 93, 1043-1065.

16. Little, J.; Shure, L. Signal Processing Toolbox for Use with Matlab. User's Guide. Mathworks: Natick, MA, 1992.

17. Pikovsky, A.; Rosenblum, M.; Kurths, J. Synchronization. A Universal Concept in Nonlinear Science. Cambridge University Press, 2001.

18. Rosenblum, M. G.; Kurths, J. Analysing Synchronization Phenomena from Bivariate Data by Means of the Hilbert Transform. In Nonlinear Analysis of Physiological Data. Kantz, H.; Kurths, J.; Mayer-Kress, G., Eds.; Springer: Berlin, 1998, p 91-99.

19. Rzeczinski, S.; Janson, N. B.; Balanov, A. G.; McClintock, P. V. E. Regions of cardiorespiratory synchronization in humans under paced respiration. Physical Review E 2002, 66, -.

20. Rosenblum, M. G.; Pikovsky, A. S.; Kurths, J.; Schafer, C.; Tass, P. Phase Synchronization: From Theory to Data Analysis. In Handbook of Biological Physics. Moss, F.; Gielen, S., Eds.; Elsevier Science, 2001, p 279-321.

21. Otnes, R.; Enochson, L. Digital Time Series Analysis. John Wiley & Sons: New York, 1972.

22. Strogatz, S. H. Nonlinear Dynamics and Chaos. Addison-Wesley, 1994.

23. Blekhman, I. I. Synchronization in Science and Technology. ASME Press: New York, 1988.

24. Pincus, S. M. Approximate Entropy as a Measure of System-Complexity. Proceedings of the National Academy of Sciences of the United States of America 1991, 88, 2297-2301.

25. Richman, J. S.; Moorman, J. R. Physiological time-series analysis using approximate entropy and sample entropy. American Journal of Physiology-Heart and Circulatory Physiology 2000, 278, H2039-H2049.

26. Grassberger, P.; Schreiber, T.; Schaffrath, C. Nonlinear Time Sequence Analysis. Int J Bifurcation Chaos Appl Sci Eng 1991, 1, 521-547.

27. Costa, M.; Goldberger, A. L.; Peng, C. K. Multiscale entropy analysis of biological signals. Physical Review E 2005, 71, -.

28. Niskanen, J. P.; Tarvainen, M. P.; Ranta-Aho, P. O.; Karjalainen, P. A. Software for advanced HRV analysis. Computer Methods and Programs in Biomedicine 2004, 76, 73-81.

29. Goldberger, A. L.; Amaral, L. A. N.; Glass, L.; Hausdorff, J. M.; Ivanov, P. C.; Mark, R. G.; Mietus, J. E.; Moody, G. B.; Peng, C. K.; Stanley, H. E. PhysioBank, PhysioToolkit, and PhysioNet - Components of a new research resource for complex physiologic signals. Circulation 2000, 101, E215-E220.

30. Novak, V.; Novak, P.; Dechamplain, J.; Leblanc, A. R.; Martin, R.; Nadeau, R. Influence of Respiration on Heart-Rate and Blood-Pressure Fluctuations. Journal of Applied Physiology 1993, 74, 617-626.

31. Hurtado, J. M.; Rubchinsky, L. L.; Sigvardt, K. A. Statistical Method for Detection of Phase-Locking Episodes in Neural Oscillations. J Neurophysiol 2004, 91, 1883-1898.

32. Lotric, M. B.; Stefanovska, A. Synchronization and modulation in the human cardiorespiratory system. Physica a-Statistical Mechanics and Its Applications 2000, 283, 451-461.

33. Entwistle, M.; Bandrivskyy, A.; Musizza, B.; Stefanovska, A.; McClintock, P.; Smith, A. Synchronization and directionality in cardio-respiratory oscillations in anaesthesia: a preliminary observational study in human males. British Journal of Anaesthesia 2004, 93, 608p-609p.

34. Kanters, J. K.; Hojgaard, M. V.; Agner, E.; HolsteinRathlou, N. H. Influence of forced respiration on nonlinear dynamics in heart rate variability. American Journal of Physiology-Regulatory Integrative and Comparative Physiology 1997, 41, R1149-R1154.

35. Suki, B.; Alencar, A. M.; Sujeer, M. K.; Lutchen, K. R.; Collins, J. J.; Andrade, J. S.; Ingenito, E. P.; Zapperi, S.; Stanley, H. E. Life-support system benefits from noise. Nature 1998, 393, 127-128.

36. Brewster, J. F.; Graham, M. R.; Mutch, W. A. C. Convexity, Jensen's inequality and benefits of noisy mechanical ventilation. Journal of the Royal Society Interface 2005, 2, 393-396.

37. Suki, B.; Arold, S. P.; Alencar, A. M.; Lutchen, K. R.; Ingenito, E. P. Noisy Ventilation Improves Lung Function. In: Unsolved Problems of Noise and Fluctuations. AIP Conf. Proc., 2003; pp 400-407.

38. Mutch, W. A. C.; Harms, S.; Graham, M. R.; Kowalski, S. E.; Girling, L. G.; Lefevre, G. R. Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung. American Journal of Respiratory and Critical Care Medicine 2000, 162, 319-323.

39. Mutch, W. A. C.; Eschun, G. M.; Kowalski, S. E.; Graham, M. R.; Girling, L. G.; Lefevre, G. R. Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia. British Journal of Anaesthesia 2000, 84, 197-203.

40. Godin, P. J.; Fleisher, L. A.; Eidsath, A.; Vandivier, R. W.; Preas, H. L.; Banks, S. M.; Buchman, T. G.; Suffredini, A. F. Experimental human endotoxemia increases cardiac regularity: Results from a prospective, randomized, crossover trial. Critical Care Medicine 1996, 24, 1117-1124.

41. Seely, A. J. E.; Christou, N. V. Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. Critical Care Medicine 2000, 28, 2193-2200.

42. Goldberger, A. L.; Amaral, L. A. N.; Hausdorff, J. M.; Ivanov, P. C.; Peng, C. K.; Stanley, H. E. Fractal dynamics in physiology: Alterations with disease and aging. Proceedings of the National Academy of Sciences of the United States of America 2002, 99, 2466-2472.

Fig. 1

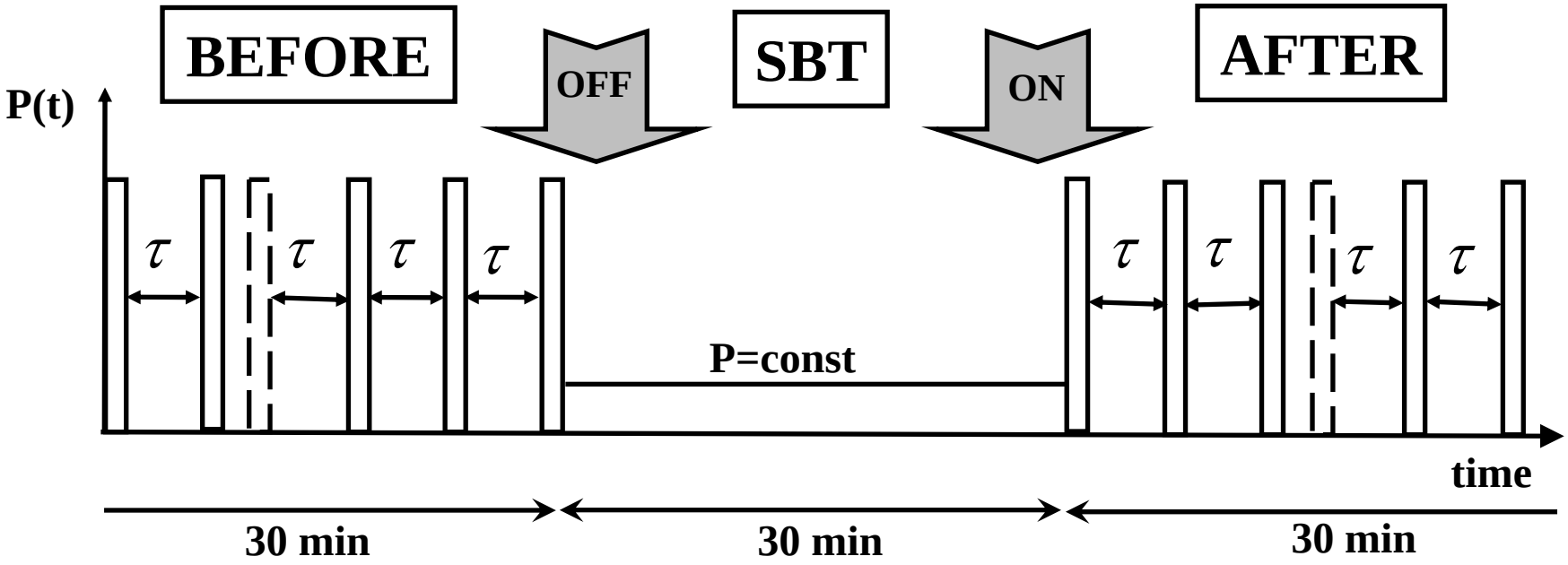
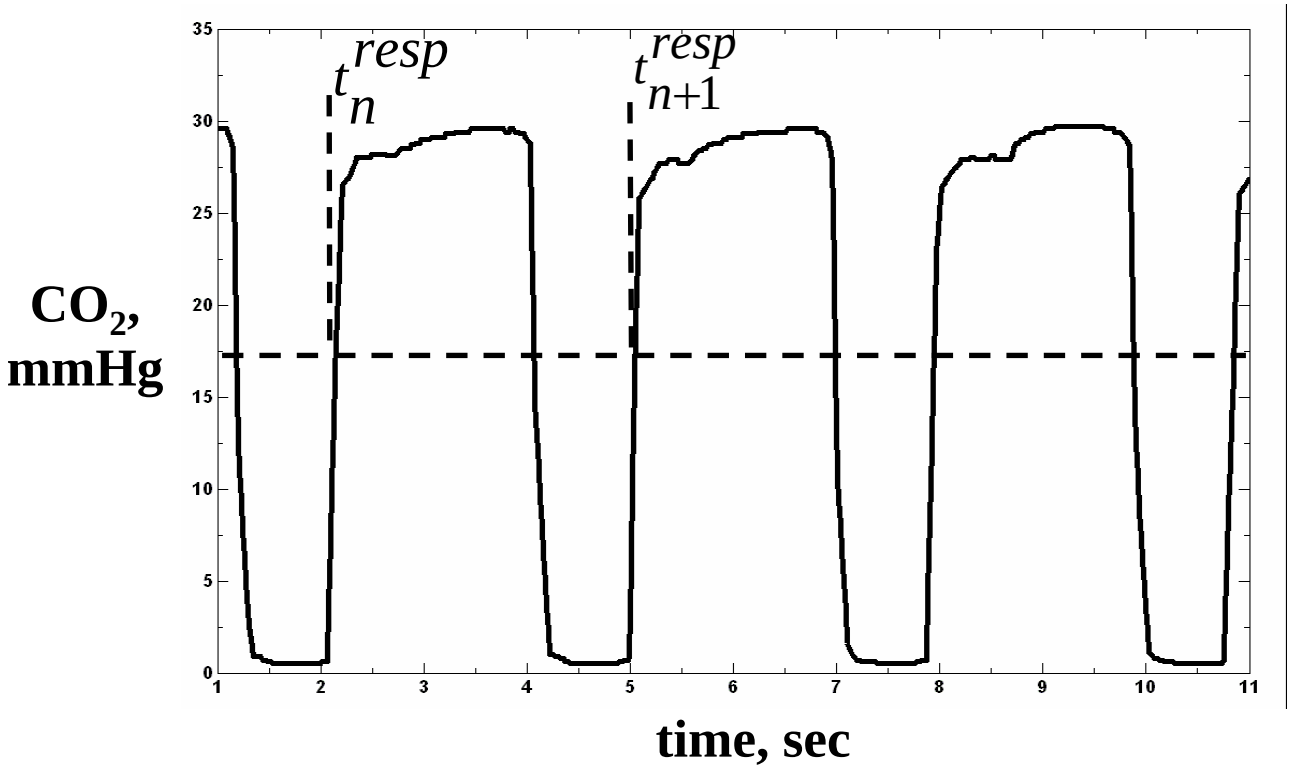

BEFORE
OFF
SBT
ON
AFTER
P(t)
τ
τ
τ
τ
P=const
τ
τ
τ
τ
time
30 min
30 min
30 min

Fig. 2


t^{resp}_{n}
t^{resp}_{n+1}
CO_2, mmHg
time, sec

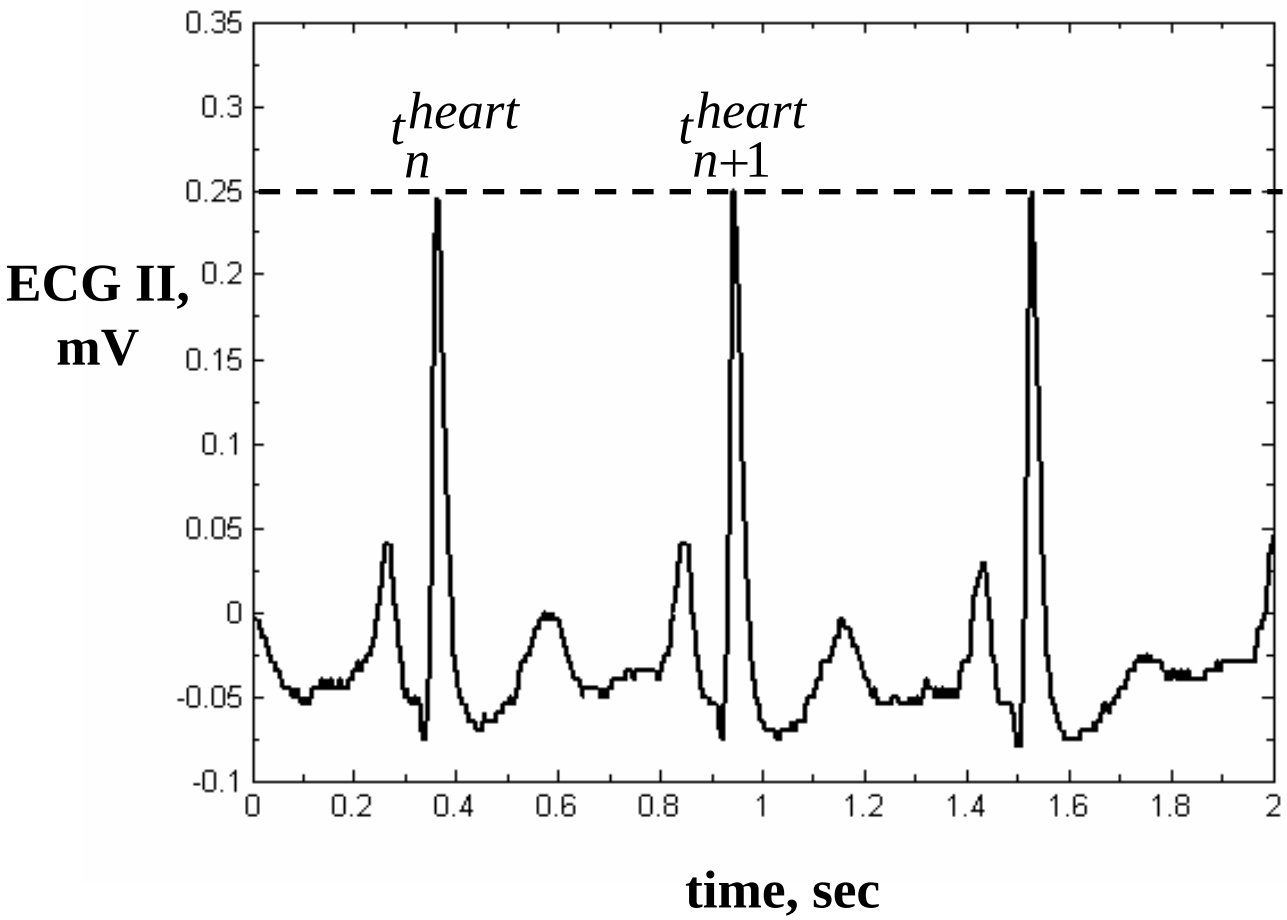
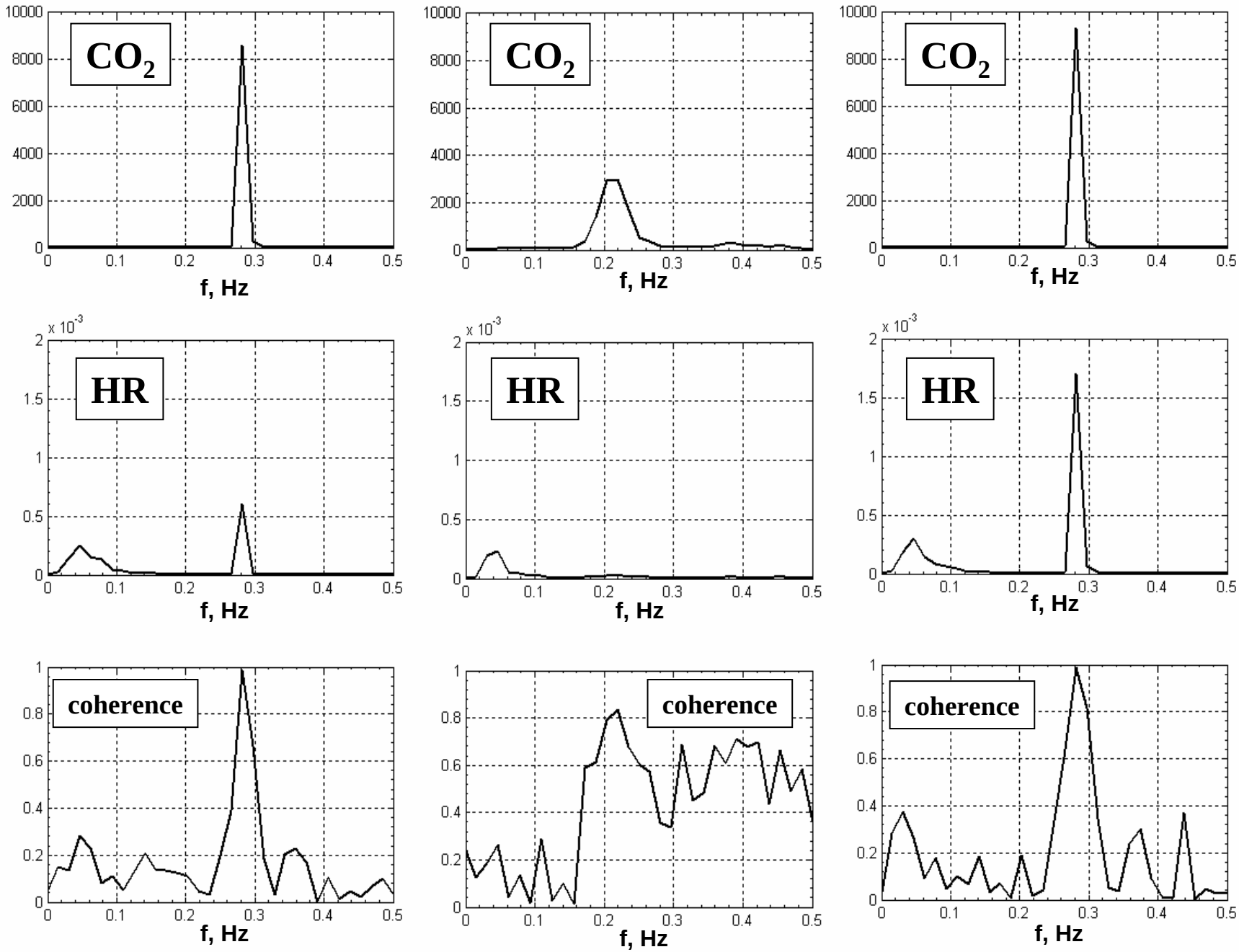

t^{heart}_{n}
t^{heart}_{n+1}
ECG II, mV
time, sec

Fig. 3



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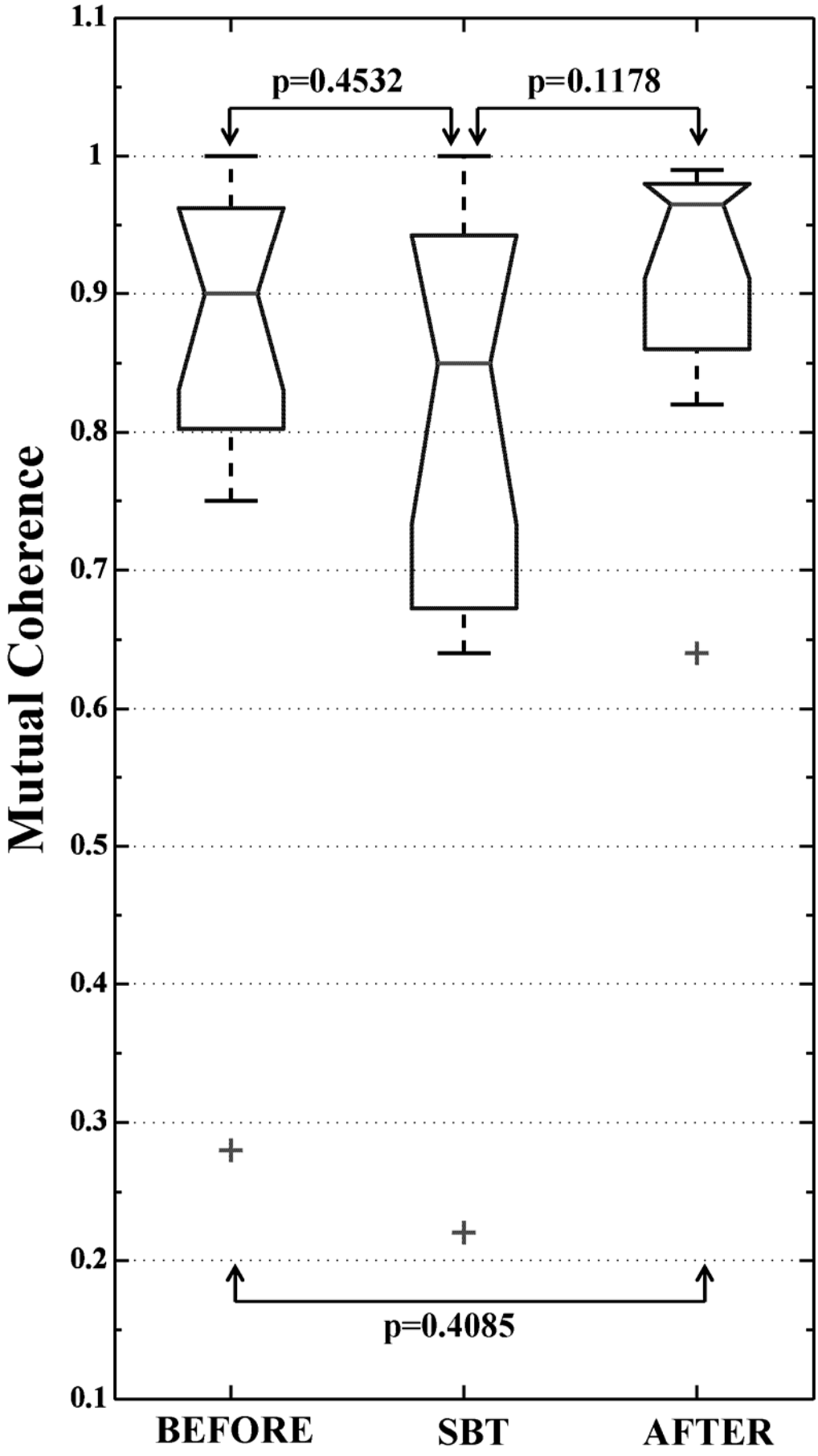
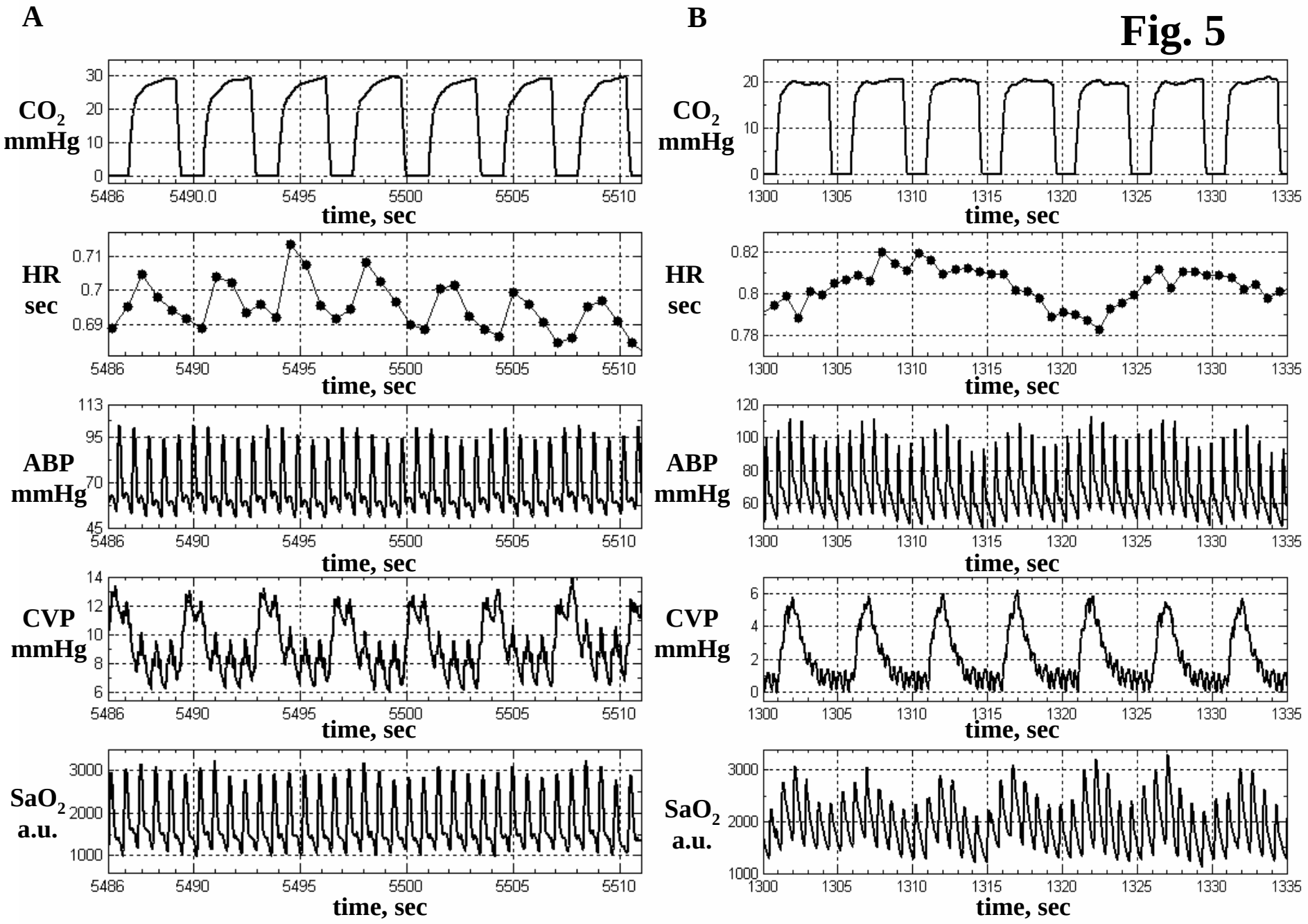

p=0.4532
p=0.1178
p=0.4085
Mutual Coherence
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
BEFORE
SBT
AFTER

Fig. 5



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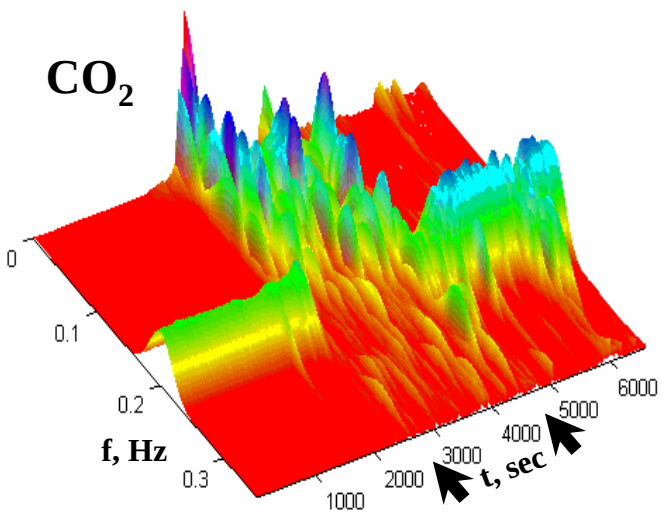
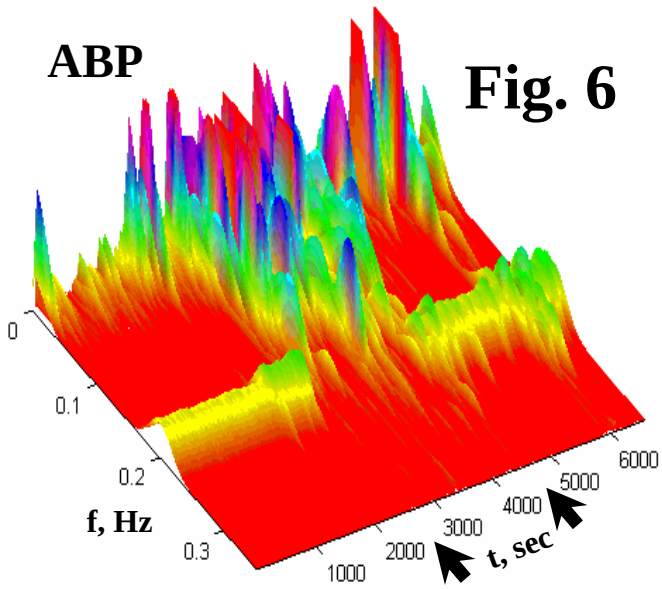
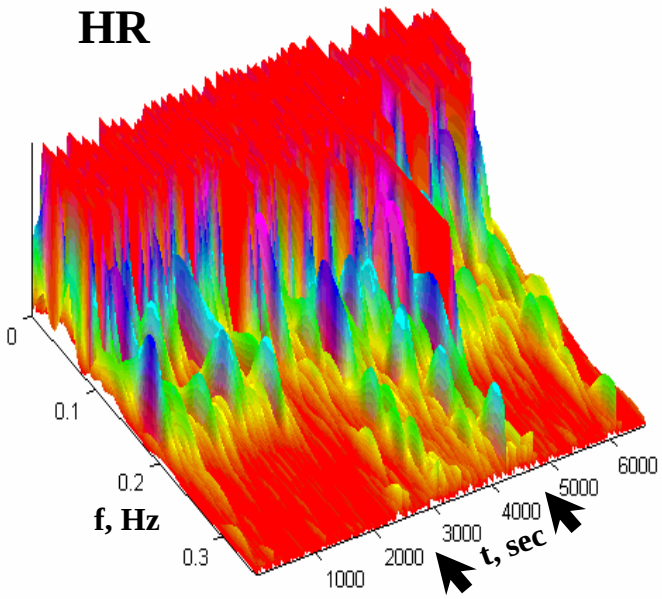
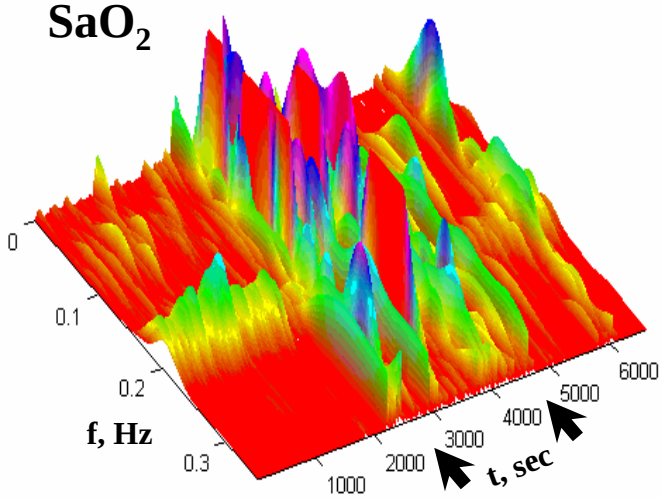

CO_2
0
0.1
0.2
0.3
f, Hz
1000
2000
3000
4000
5000
6000
t, sec


ABP
0
0.1
0.2
0.3
f, Hz
1000
2000
3000
4000
5000
6000
t, sec


HR
0
0.1
0.2
0.3
f, Hz
1000
2000
3000
4000
5000
6000
t, sec


SaO_2
0
0.1
0.2
0.3
f, Hz
1000
2000
3000
4000
5000
6000
t, sec

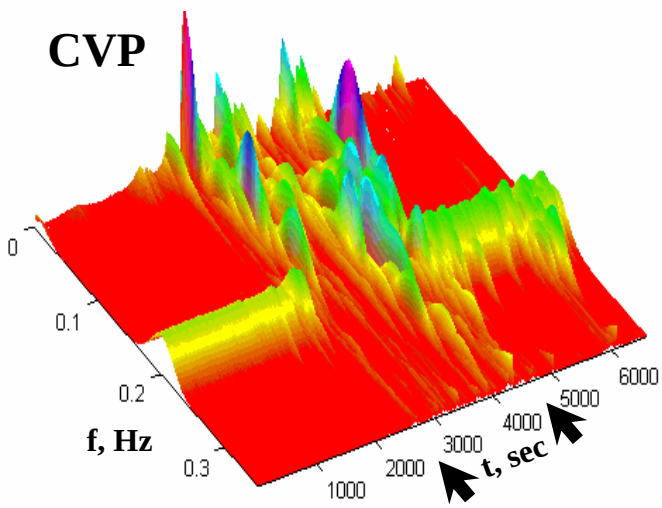

CVP
0
0.1
0.2
0.3
f, Hz
1000
2000
3000
4000
5000
6000
t, sec

Fig. 7

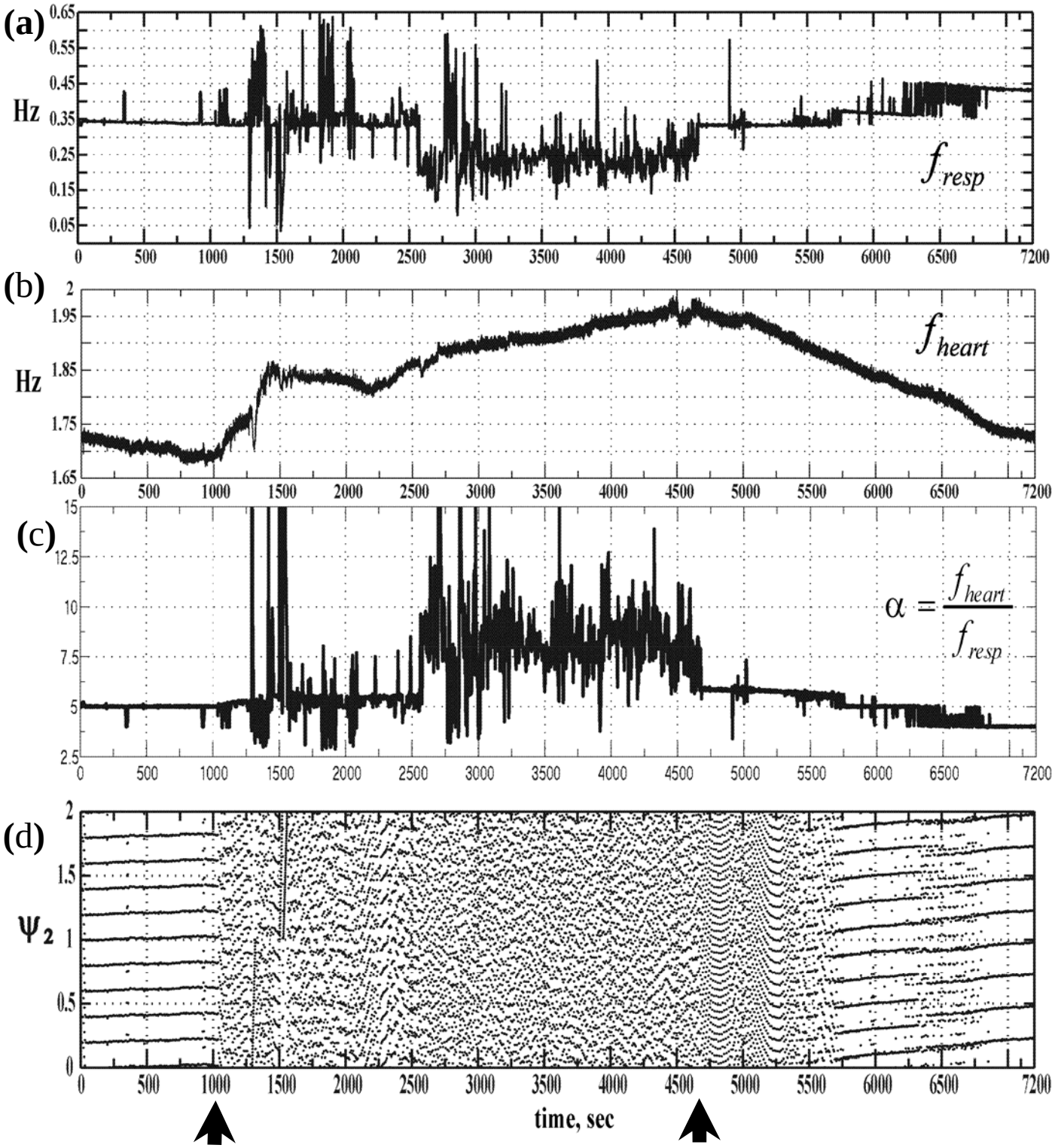

(a)
Hz
f_{resp}
(b)
Hz
f_{heart}
(c)
$\alpha = \frac{f_{heart}}{f_{resp}}$
(d)
ψ_2
time, sec

Fig. 8

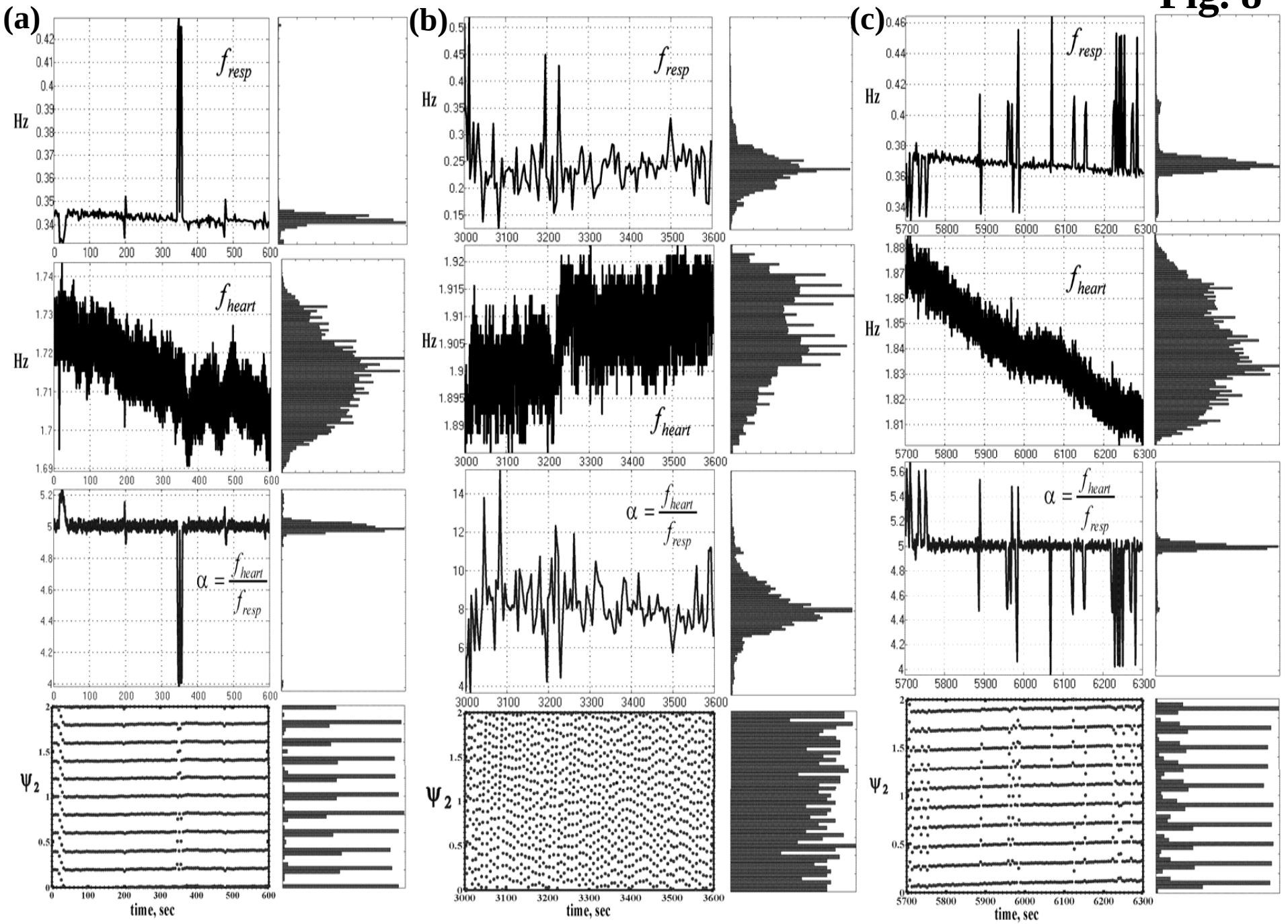


Fig. 9

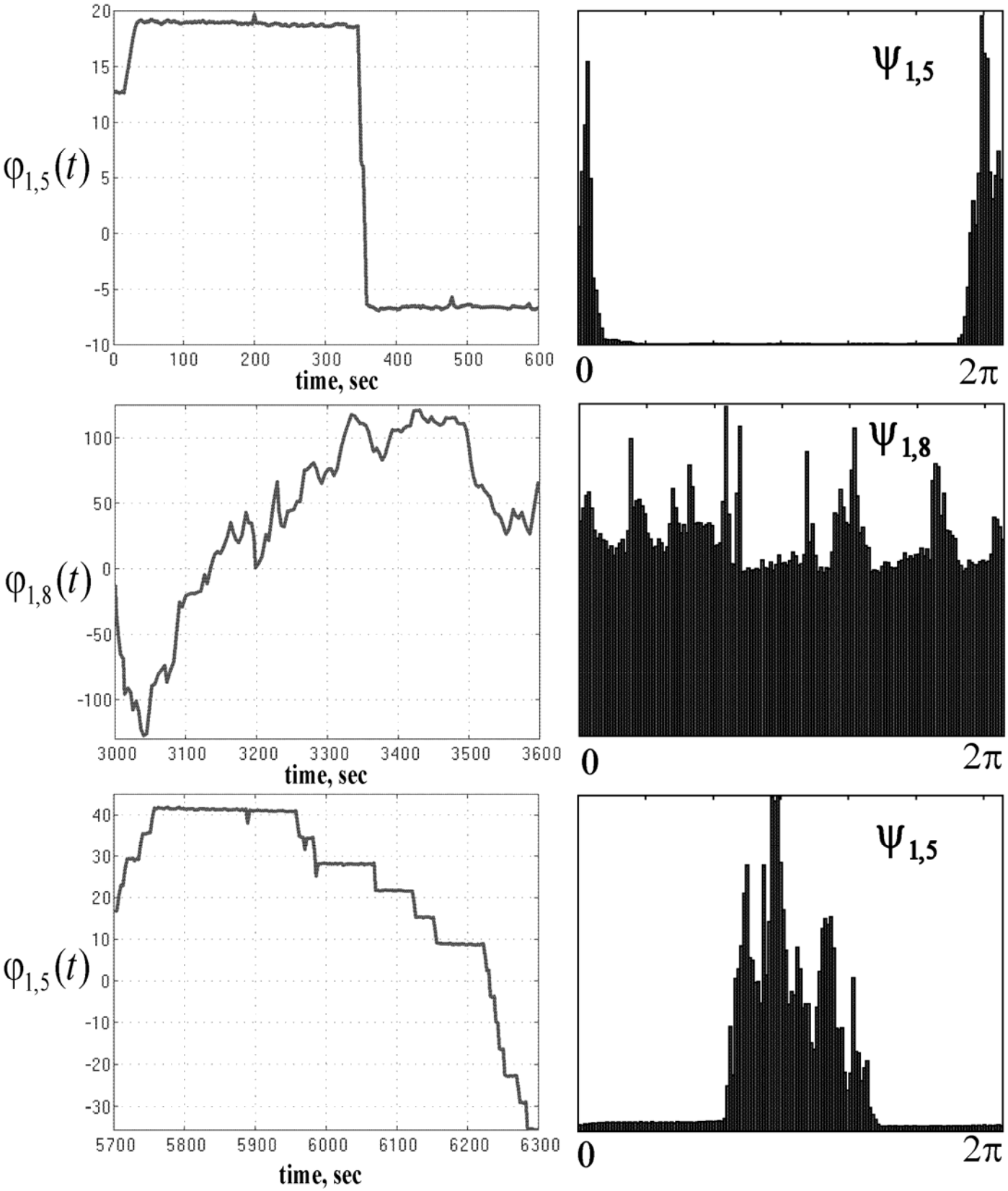
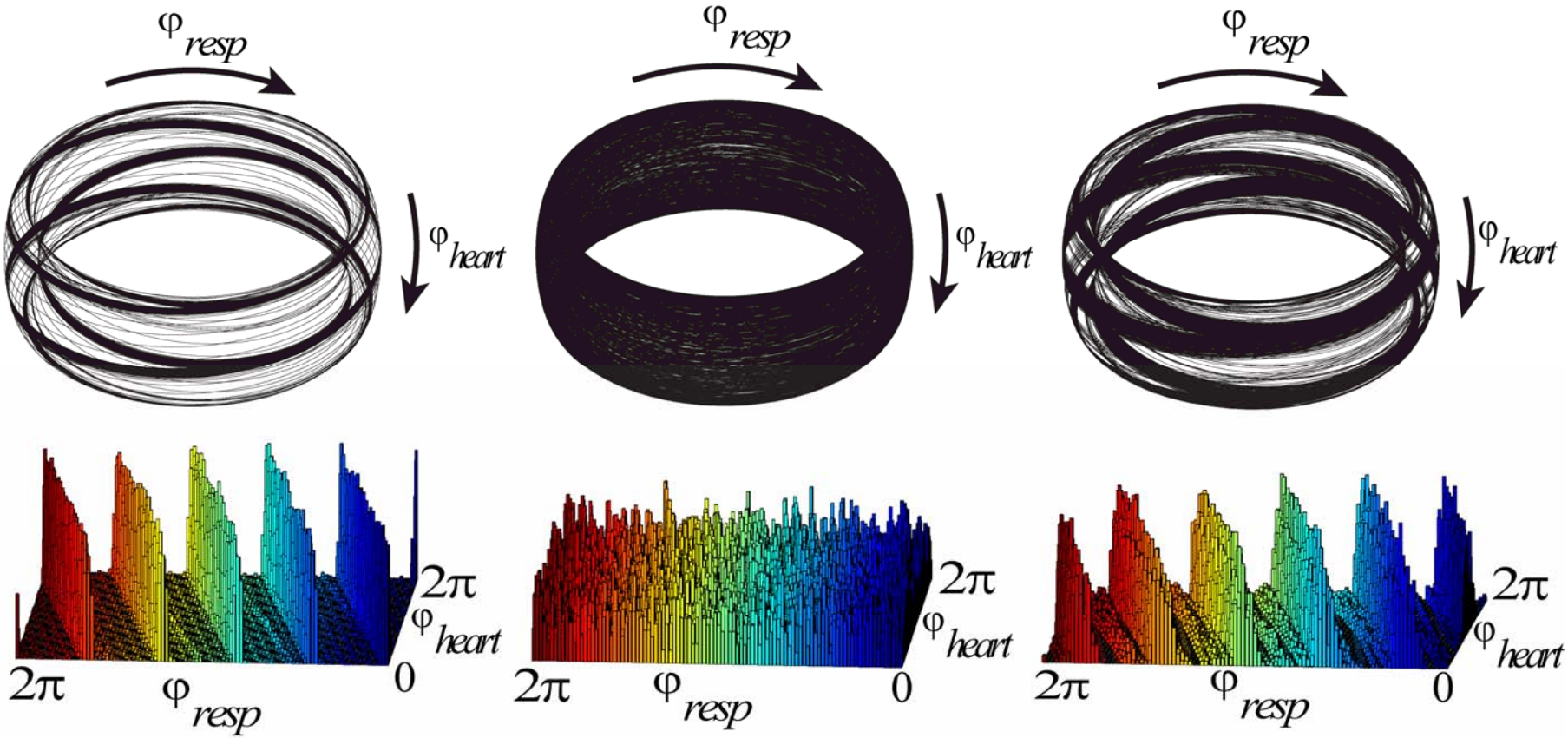

$\varphi_{1,5}(t)$
time, sec
$\psi_{1,5}$
0
2π
$\varphi_{1,8}(t)$
time, sec
$\psi_{1,8}$
0
2π
$\varphi_{1,5}(t)$
time, sec
$\psi_{1,5}$
0
2π

Fig. 10



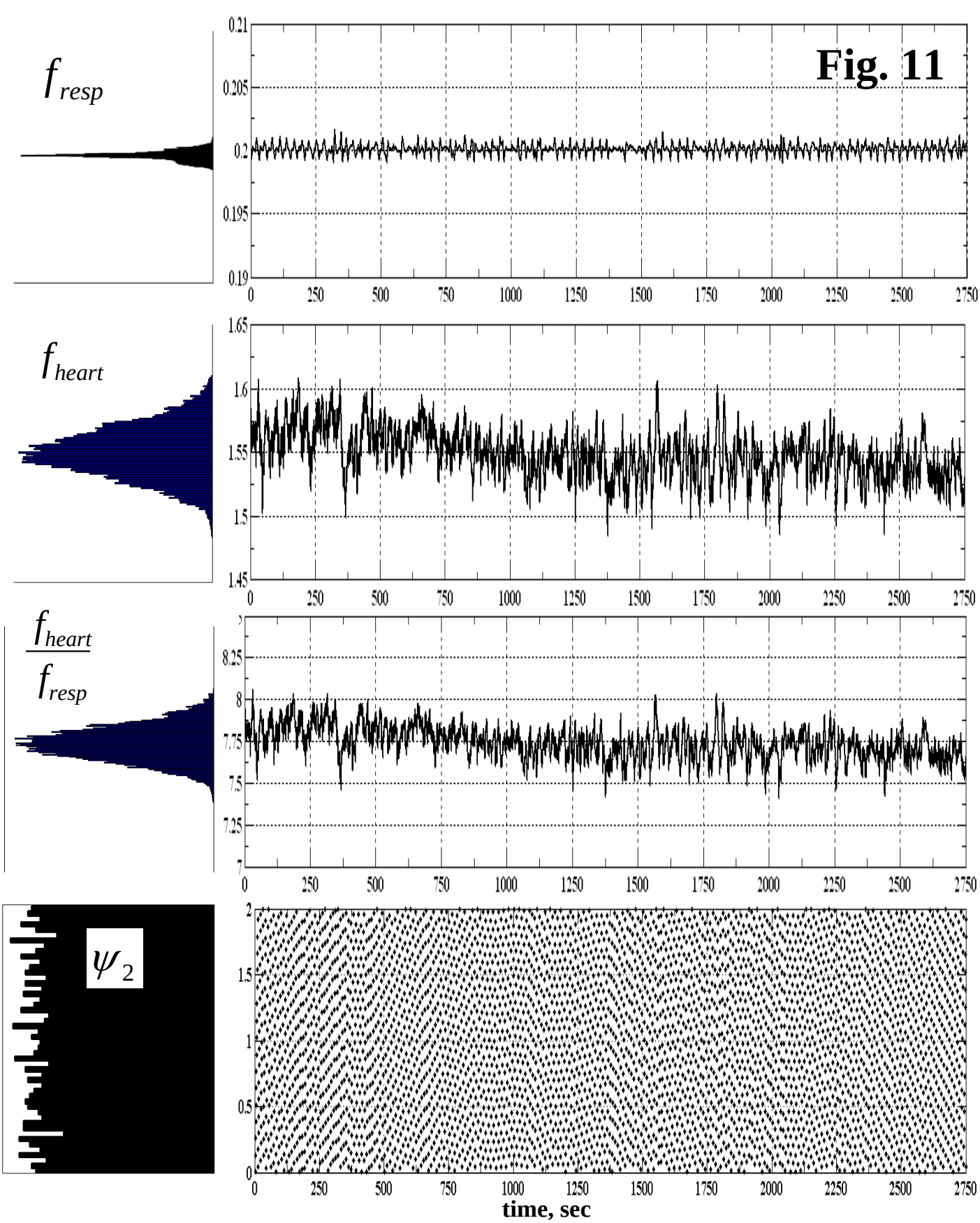
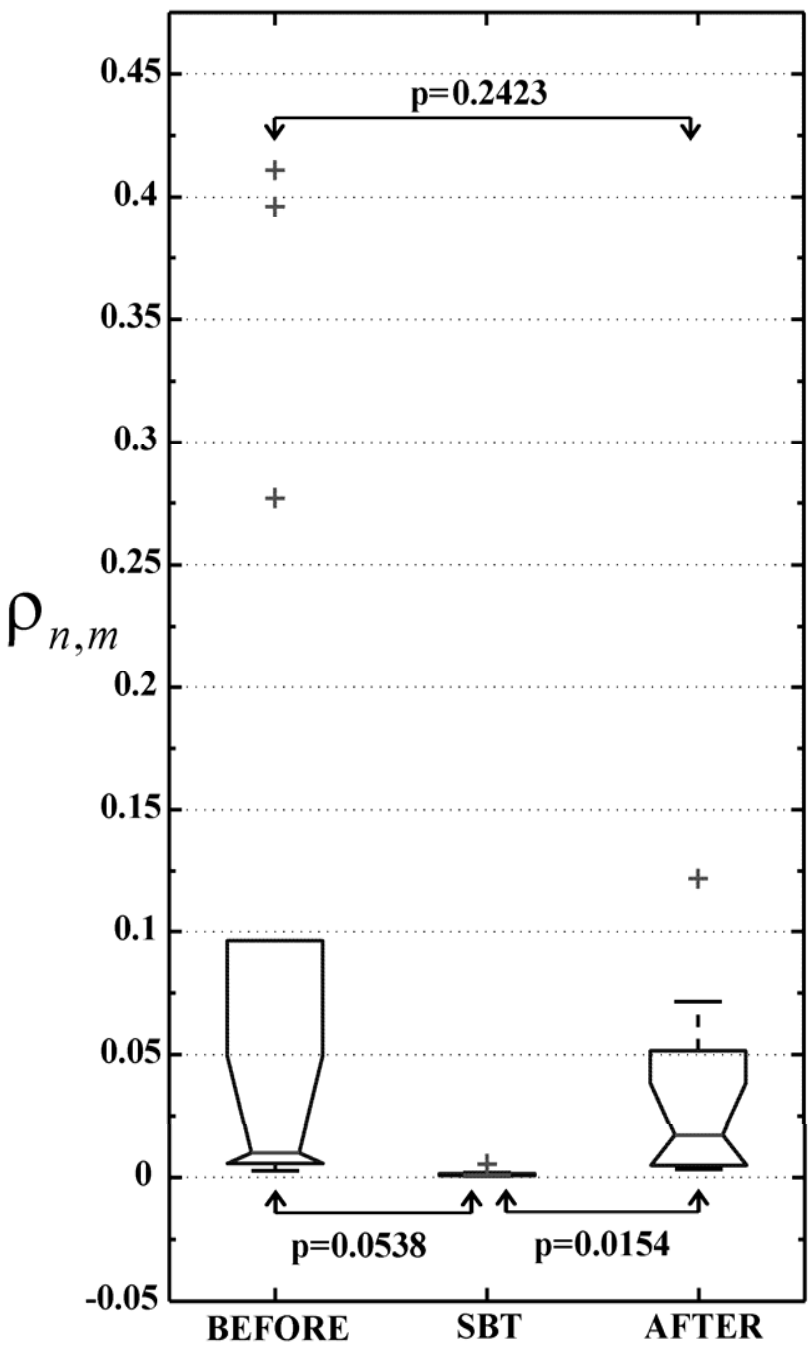

f_{resp}
0.21
0.205
0.2
0.195
0.19
0 250 500 750 1000 1250 1500 1750 2000 2250 2500 2750
f_{heart}
1.65
1.6
1.55
1.5
1.45
0 250 500 750 1000 1250 1500 1750 2000 2250 2500 2750
$\frac{f_{heart}}{f_{resp}}$
8.25
8
7.75
7.5
7.25
7
0 250 500 750 1000 1250 1500 1750 2000 2250 2500 2750
ψ_2
2
1.5
1
0.5
0
0 250 500 750 1000 1250 1500 1750 2000 2250 2500 2750
time, sec

Fig. 11

Fig. 12


0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
$\rho_{n,m}$
p=0.2423
p=0.0538
p=0.0154
BEFORE
SBT
AFTER

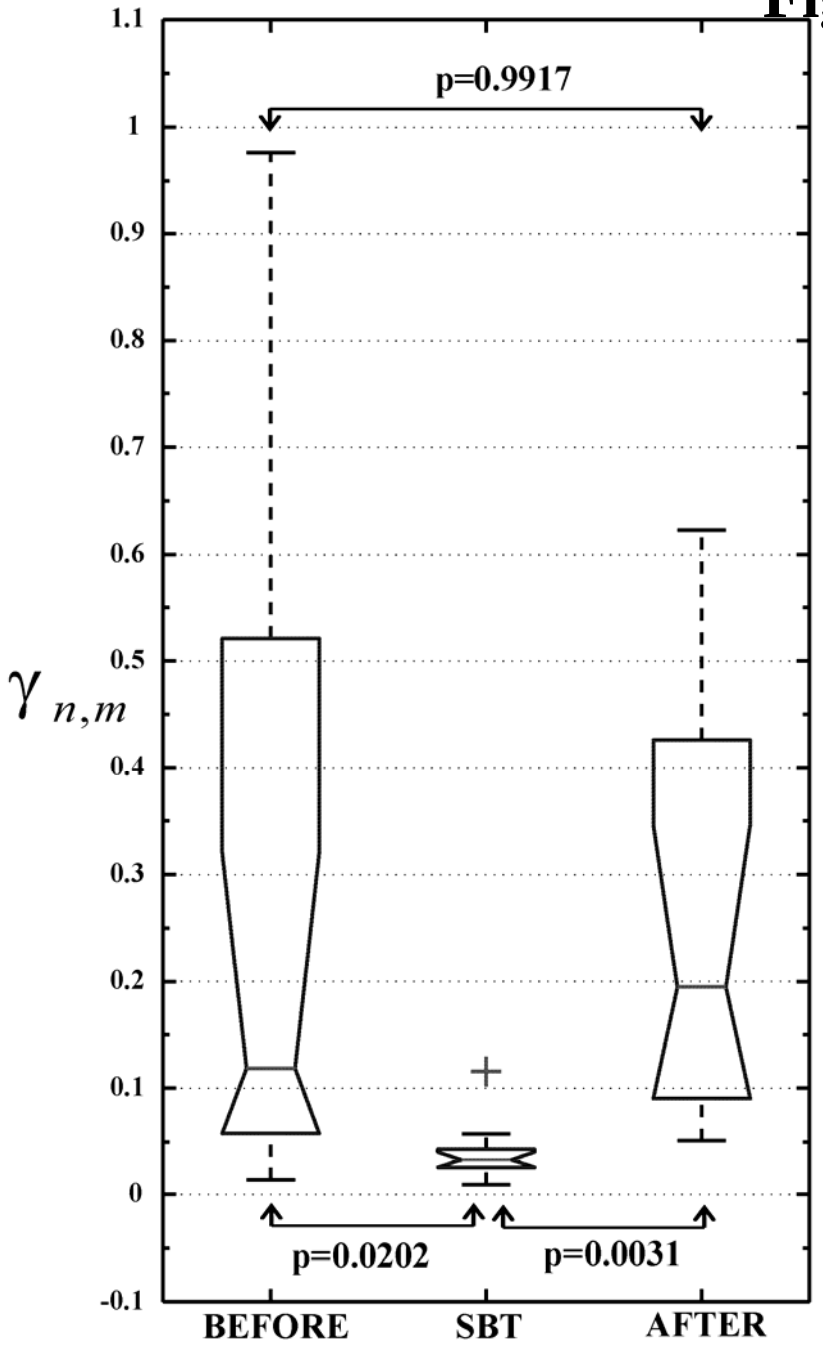

1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
$\gamma_{n,m}$
p=0.9917
p=0.0202
p=0.0031
BEFORE
SBT
AFTER

Fig. 13

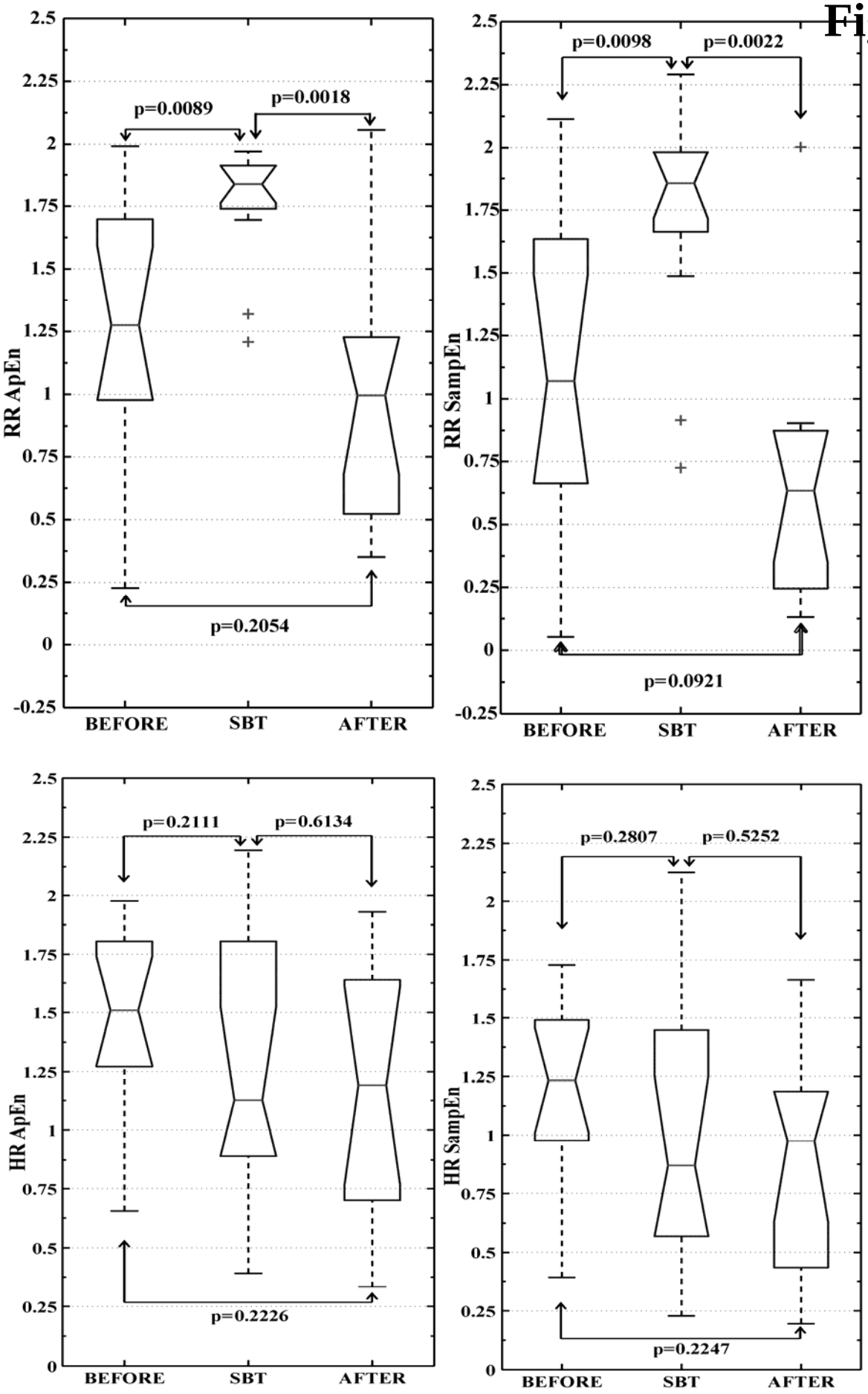
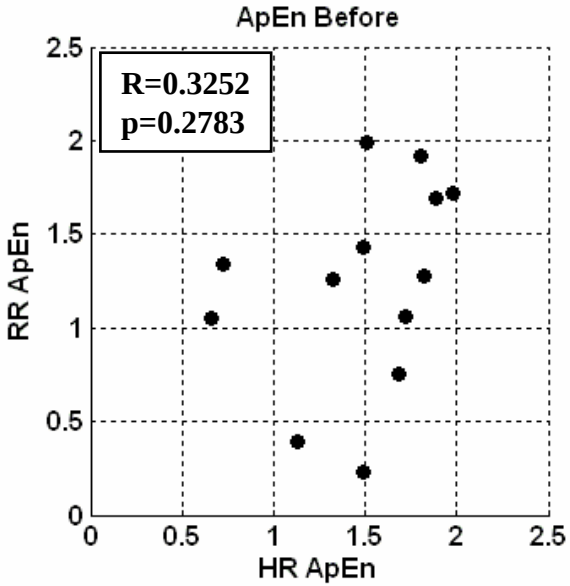
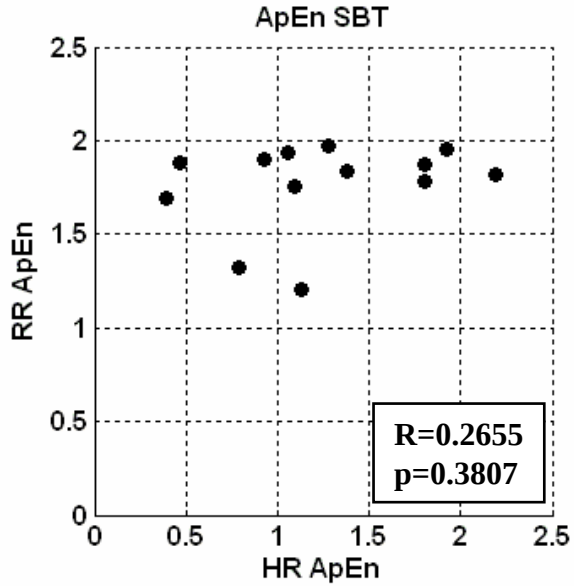
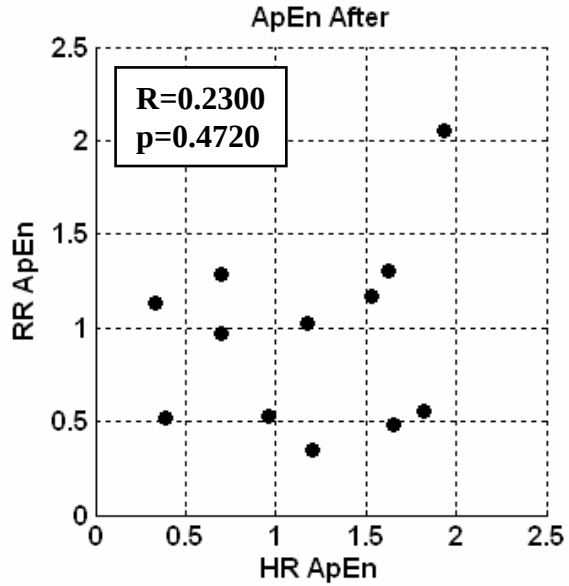
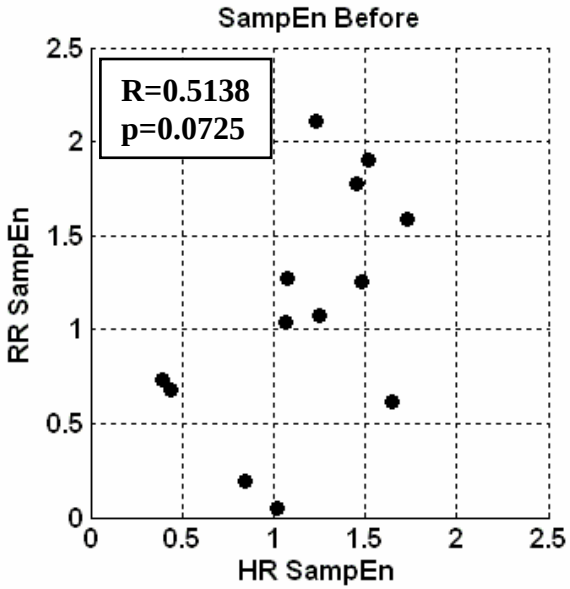

RR ApEn
p=0.0089
p=0.0018
p=0.2054
BEFORE
SBT
AFTER
RR SampEn
p=0.0098
p=0.0022
p=0.0921
HR ApEn
p=0.2111
p=0.6134
p=0.2226
HR SampEn
p=0.2807
p=0.5252
p=0.2247

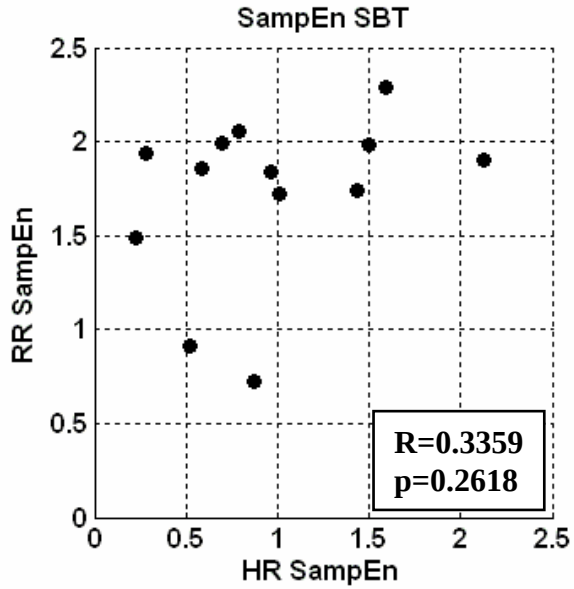
Fig. 14


ApEn Before
R=0.3252
p=0.2783
RR ApEn
HR ApEn


ApEn SBT
R=0.2655
p=0.3807
RR ApEn
HR ApEn


ApEn After
R=0.2300
p=0.4720
RR ApEn
HR ApEn


SampEn Before
R=0.5138
p=0.0725
RR SampEn
HR SampEn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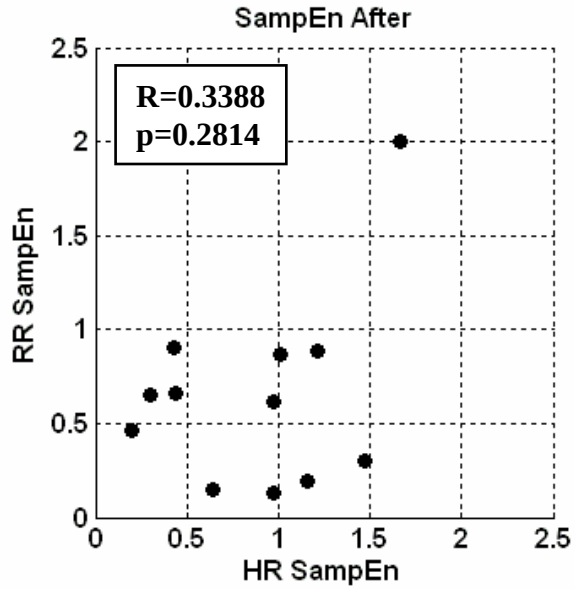
RR SampEn
HR SampEn


SampEn After
R=0.3388
p=0.2814
RR SampEn
HR SampEn

Buchman, Timothy

From: complexity2@comcast.net
Sent: Tuesday, February 05, 2008 10:24 AM
To: buchman@wustl.edu
Subject: review of your ms, RA-07-739

Attachments: ref#1RA-07-739.doc

ref#1RA-07-739.doc (20 KB)

Re: Cardiorespiratory Dynamics During Transitions Between Mechanical and Spontaneous Ventilation in Intensive Care

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